Letters

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Time to talk about rape

Women must be free to take charge of their own lives

EDITOR—A campaign against rape is needed that is based on the human rights of women in their own right rather than on their relationship to the men in their lives.

Although I am pleased to see rape on the agenda for discussion, I feel that the approach taken by MacDonald fails to reflect the reality of women's lives in the countries she mentions.[1] It is useless to say that men should remember that women are their mothers, wives, and daughters when husbands, fathers, grandfathers, and brothers commit a large proportion of rape and violence against women. The family home may well be the least safe place for a woman to be. It is common in some communities for a woman to be forced into marriage with her rapist as a means of safeguarding what is regarded as the family honour.

In a study of convicted perpetrators of child sexual abuse in London, 57% of the female victims were abused by relatives or within the home.[2] Of the perpetrators, 15.5% sexually abused their natural daughters, 10.5% sexually abused their stepdaughters, and 10% abused other female relatives. In a study of rape conducted in London by questionnaire, of 694 woman who completed the questionnaire, 11% reported being raped by a family member, 10% by a boyfriend or former boyfriend, and 5% by a family friend.[3] Women must be free to take charge of their own lives and to choose their place of work without discrimination and, if they wish to marry, to choose their own marriage partners. Until this happens a woman will be perceived as the property of a male and her value will be judged by her virginity or her chastity. Until society eschews all violence against women and grants them the same rights as men to education, work, and personal freedom, women will be raped twice—the first time by their assailant and the second time by the legal system that tries the case.

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1 MacDonald R. Time to talk about rape. *BMJ* 2000;321: 1034-5. (28 October.)
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Joint initiatives can improve services for complainants of sexual assault

EDITOR—We endorse MacDonald's recent editorial on sexual assault and violence against women.[1] Though the global statistics on sexual assault against women are shocking, we should not ignore the facts that are closer to home. In the year 1999-2000, 2300 allegations of rape were made to the Metropolitan Police Force of London.[2] Since 1985 the number of allegations of rape has increased threefold, which mirrors the worldwide situation. Despite the increase in reported rapes the crime is underreported and conviction rates have dropped (K Giles, New Scotland Yard, personal communication). The percentage of court cases that secured a conviction for rape has decreased from 24% to 9% in the past 15 years.[3]

To improve the service provided by the police to adult complainants of sexual assault, a new project has been piloted by the Metropolitan Police in southeast London. The Haven has been set up between the Metropolitan Police and King's College Hospital NHS Trust to provide comprehensive care for female and male victims of sexual assault and rape. The Haven can be accessed 24 hours a day, seven days a week by victims themselves or via the police. It is set in a self contained unit within the sexual health department of King's College Hospital rather than in a police station. The service provides forensic medical examinations for victims and can offer immediate medical care, such as first aid; prophylaxis against infections, including HIV; and emergency contraception.

The Haven also runs three follow up clinics a week where psychosocial support and counselling contracts of six sessions are offered, together with screening for sexually transmitted diseases, including HIV testing. Since its launch in May 2000, the centre has seen 320 people, of whom the police referred 253. Nineteen of the complainants were male, and 40 were aged between 12 and 15 years.

The Haven is based on the pioneering service at St Mary's Hospital in Manchester but integrated into a comprehensive sexual health service. The Haven aims to provide victims of sexual assault with a sensitive environment that supports reporting to the police, optimises collection of forensic evidence, and offers continuing medical and psychosocial support.

We hope that the Haven will advance the service available to complainants of sexual assault, thereby encouraging reporting to the police, which in turn may improve conviction rates in sexual offences.

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Chemotherapy for advanced colorectal cancer

Please aim for accuracy rather than hard hitting headlines

EDITOR—Michael and Zalcberg's editorial on chemotherapy for advanced colorectal cancer and the Colorectal Cancer Collaborative Group's systematic review of palliative chemotherapy for advanced colorectal cancer agree superficially.[1 2] This makes the discrepancy between their conclusions surprising and raises certain questions of accuracy

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and presentation. The editorial overplays the value of such treatment, which was more scientifically assessed by the paper.

Firstly, the editorial's statement that there is a 35% reduction in the risk of death for treated patients is an oversimplification of the results. In the systematic review, from which this conclusion was derived, fig 2 unambiguously shows that the risk of death is only about 16% less in the treated group.[2] This translates to a median survival advantage of only four months and applies only to a period between 5 and 15 months from the start of treatment. This summary is more accurate than the one derived from the more complicated and inferred statistics used in the editorial.

Secondly, the editorial tries to make a case for a palliative value of the treatment where the paper fails to find such a benefit. It makes that case for two subgroups of patients in single studies (references 4, 5, 6 in the editorial corresponding to references 15, 22, 17 in the paper). The result of this "splitting" contradicts the overall result in the paper: "data on the effect of chemotherapy on quality of life are inadequate to draw firm conclusions about the palliative benefit of chemotherapy."

Thirdly, the editorial glosses over the toxicity of chemotherapy, which could not be meaningfully summarised in the systematic review.[2] Additionally, the literature possibly underestimates the toxicity of chemotherapy in view of the relatively younger population of the reviewed studies.

The editorial lacks the expected balance of opinion. The impact of an editorial with a gripping headline in a journal such as the *BMJ* should be more seriously considered. The now freely available access to such an unbalanced message can lead to conflict between a terminally ill and vulnerable group of patients and their medical carers, resulting in unnecessary suffering and a possible break of trust.

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Competing interests: None declared.

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2 Colorectal Cancer Collaborative Group. Palliative chemotherapy for advanced colorectal cancer: systematic review and meta-analysis. *BMJ* 2000;321:531-5. (2 September.)

Does the evidence or the doctor have the greater influence?

Editor—The editorial by Michael and Zalcberg on chemotherapy for advanced colorectal cancer[1] differed in its conclusions from the Colorectal Cancer Collaborative Group's systematic review and meta-analysis.[2] The systematic review showed a modest improvement in median survival but no clear evidence on the effects on symptom control, treatment toxicity, or quality of life. In contrast, the editorial concluded that chemotherapy, as well as increasing median survival, also has palliative benefits. Might this difference be accounted for by the fact that Michael and Zalcberg made their assessment of the evidence through the eyes of "believers" in chemotherapy for advanced colorectal cancer?

Since experts do not agree on what the evidence shows concerning the benefits of these treatments, how can patients make an informed decision, as Michael and Zalcberg suggest they should? The patients' task is especially difficult as they face the psychological stress of an illness that will lead to their death, probably within months, whether or not they opt for chemotherapy.

Is it not also true that the mode of presentation of the evidence is as likely to affect the patients' decision as the facts themselves, if not more so? It is current practice for medical journals to publish a note on any competing interests that might affect the authors' role as independent observers and reporters, so that readers can take this into account in their assessment of the authors' conclusions. How often do we admit such competing interests to patients when "selling" treatments? Not acknowledging such interests to patients may introduce a subtle paternalism, while we congratulate ourselves that we allow patients to make their "informed" decisions.

This inherent problem highlights the importance of multidisciplinary teams, which include palliative care specialists, to help balance out such a situation. As they make their difficult decision, patients need to be counselled by team members who can give them sufficient time and ongoing support and who can honestly acknowledge that the evidence is at best unclear.

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2 Colorectal Cancer Collaborative Group. Palliative chemotherapy for advanced colorectal cancer: systematic review and meta-analysis. *BMJ* 2000;321:531-5. (2 September.)

Authors' reply

Editor—Much of cancer treatment, especially chemotherapy for metastatic disease, is prescribed with palliative intent—that is, improvement in the quality of survival. Evidence of any improvement in the duration of survival has been elusive, so improvement in quality of life has been the more realistic goal of such treatment; hence the importance of a meta-analysis (justifying the "hard hitting headlines") that clearly shows longer survival in patients with metastatic colorectal cancer. It is regrettable that the use of standard terminology in describing these survival benefits offends Kirollos, as this approach to reporting odds ratios is in widespread use.

Any meta-analysis is limited by the studies on which it is based. As our editorial stated, the meta-analysis by the Colorectal Cancer Collaborative Group evaluated 13 trials, of which only 10 were randomised. There was significant heterogeneity in the regimens used. Supportive interventions and the extent of crossover were not detailed. Despite these shortcomings a clear survival benefit due to chemotherapy was shown (which, given the nature of the trials considered, is most probably underestimated), with less clear cut palliative benefits.

Because of the trial design and the difficulty in measuring quality of life, palliative benefit without significant toxicity could not be defined by this meta-analysis. But does this imply a lack of such a benefit? The three studies of asymptomatic patients were well designed and used validated instruments for the assessment of palliative benefit and treatment toxicity.[1–3] Their findings showed the significant palliative benefits of systemic treatment in this disease despite the well known toxicities of treatment. This result is in keeping with similar findings observed in other malignancies.[4 5]

An observant policy, systemic chemotherapy, or measures to control symptoms should be considered among the wider range of options available to patients with advanced colorectal cancer. The aim of chemotherapy in this disease is to provide patients with a realistic therapeutic option while taking into account their personal wishes, performance status, and medical comorbidities. Such an approach provides patients with the potential for an improved quality of life and an acceptable toxicity profile.

We agree that patients should have the opportunity to discuss the options with the relevant specialist and in the context of a multidisciplinary team approach. But to suggest that the evidence is not sufficiently rigorous to justify considering chemotherapy in all reasonably fit patients with metastatic colorectal cancer perpetuates a policy of nihilism that is unjustified.

To provide additional evidence for a meta-analysis would require further such studies. But because of the known survival benefit and quality of life benefits shown in the three studies cited above, we believe that further trials comparing chemotherapy with best supportive care for first line (and arguably second line) treatment in advanced colorectal cancer are unethical.

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Patients need time to reflect on uncertainties surrounding palliative chemotherapy

EDITOR—The Colorectal Cancer Collaborative Group concluded that "although chemotherapy can prolong life, … the median survival remains short" and suggested that further research is needed to clarify the palliative benefit of chemotherapy.[1] In their editorial, however, Michael and Zalcberg state that "there is now strong evidence to suggest that chemotherapy should be offered to all patients with advanced colorectal cancer, depending on their physical functioning."[2] The Collaborative Group's systematic review concluded that the overall quality of evidence relating to treatment toxicity, symptom control, and quality of life was poor.

Supportive care was not clearly defined in the studies reviewed in the meta-analysis.[2] If valid conclusions are to be drawn about the palliative effect of chemotherapy compared with supportive care then clear standards of palliative and supportive care need to be established and reliable quality of life and toxicity data should be available.

Michael and Zalcberg suggest that patients should be allowed to make an informed decision. How do we achieve such informed consent? Most patients with advanced cancer will accept any chemotherapy if it is offered.[3] Patients may be shocked by the news of their advanced disease and think that chemotherapy offers hope of a cure. Doctors may be reluctant to communicate the poor prognosis and to explore the uncertain impact of chemotherapy on the patient's quality of life.[4]

Oncologists and palliative care teams need to work closely together to give patients time to assimilate the bad news of their advanced cancer and an opportunity to reflect on the uncertainties surrounding palliative chemotherapy.

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Recent advances in palliative care

United Kingdom continues to lead in palliative care

EDITOR—It was disappointing to read Billings's review on palliative care.[1] Many of the so called recent advances mentioned in the first part of the article have been practised for many years in the management of British patients with a terminal condition. Much of the second half of the article does palliative care a deep injustice.

The object of good palliative care is always the alleviation of suffering; hastening death is never the intention. It is wrong to suggest that most dying patients are unable to make decisions and that dehydration with the intention of committing euthanasia is an acceptable management option.

The situation in Oregon, with the promotion of physician assisted suicide, and that in the Netherlands, with high levels of involuntary killing, are a direct consequence of poor access to good palliative care. The United Kingdom pioneered palliative care and continues to lead in it.

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Importance of palliative care for children is being increasingly recognised

EDITOR—Billings writes about the palliative care needs of adults.[1] Although fewer children than adults die, they also require palliative care. I am writing on behalf of the Palliative Care Working Group of the Royal College of Paediatrics and Child Health, which wants to alert readers to some of the special needs of children.[2 3]

The illnesses from which children die are different from those from which adults die, and paediatric palliative care has emphasised the importance of developing services for children other than just those with cancer. The need for palliative care arises in four broad groups:

- Life threatening conditions for which treatment is available but may fail—for example, cancer
- Conditions in which premature death is expected but long periods of intensive treatment to prolong good quality life are anticipated—for example, cystic fibrosis, HIV infection/AIDS
- Progressive conditions that may extend over many years and for which no curative treatment is available—for example, Batten disease, mucopolysaccharidoses
- Conditions with severe disability that, although not progressive, lead to extreme vulnerability and in which premature death is likely—for example, cerebral palsy.

The continuing physical, emotional, and cognitive development in children sets them apart from adults. It influences all aspects of their care, including pharmacological treatment, their understanding of their disease, their communication skills, and their level of dependence.

Parents are usually the main carers for children, with care taking place at home. They and the child's siblings will need support throughout the child's illness and their bereavement.

Often, many professional and voluntary agencies are involved, as skill in different aspects of paediatrics and palliative care is needed. Care in hospital, care at home, respite care, and education all need to be coordinated, and community paediatric nurses often do this as key workers.

Many children have prolonged illnesses; an integrated approach is then required, with a gradual change in the emphasis of care between treatments aiming to cure or prolong life and palliative care, rather than one having rigid boundaries.

Although palliative care for children is a relatively young specialty, its importance is being increasingly recognised. The Royal College of Paediatrics and Child Health has established a special interest group to promote the best possible care and develop medical training. Similar commitment exists in nursing. The voluntary sector contributes heavily, particularly with children's hospices, and government help has come through the "Diana nurses" project.

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How to manage the first episode of schizophrenia

Authors did not take account of systematically collected information

EDITOR—Frangou and Byrne review recent descriptive work on how to manage the first episode of schizophrenia but omit to note that some of the treatment issues discussed have been systematically investigated.[1]

The authors are apparently unaware that the efficacy of drug treatment and its correlates was examined in a controlled clinical trial following first episodes of psychosis conducted at the Medical Research Council Centre at Northwick Park.[2] This study established that by two years following discharge after the first episode, 46% of patients taking active drug treatment had relapsed compared with 62% taking placebo.[3] Response to treatment was not predicted by the features of the illness—a point of practical importance.

An important determinant of relapse was the duration of illness before the start of neuroleptic treatment, a finding that has been well established in the literature subsequently. Of those who had experienced symptoms for one year before admission, only 18% given active treatment were relapse free at two years and all the patients given placebo had relapsed. The meaning of this finding—whether long duration of illness before admission is a correlate of poor outcome or whether early treatment prevents deterioration—remains obscure.

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Other findings in this study are relevant to Frangou and Byrne's recommendations regarding family therapy.[4] Some forms of such therapy have been suggested to reduce expressed emotion in relatives and thereby to reduce the probability of relapse. In this study, when preadmission duration of illness and neuroleptic treatment were taken into account, the variables of expressed emotion were not related to outcome or to response to treatment. This suggested that such features might be a correlate of severity of illness rather than a precipitant or predictor of relapse.

Frangou works at the Institute of Psychiatry in London. When systematically collected information from a controlled trial is available I am disappointed to find that it has had little impact on recommendations regarding management from a leading academic institute.

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Competing interests: None declared.

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Innovations in service provision need evidence, not opinion

EDITOR—Yet again we read that cognitive behavioural therapy is of benefit for psychosis.[1] The authors of the editorial claim that such therapy "is useful in reducing persistent delusions and hallucinations" but in support of this statement cite a study that showed no such thing.[2]

In reality, the findings of the cited study were reported as follows: "As regards positive symptoms … there were no significant differences between the groups at any time point." If there is evidence to support the efficacy of cognitive behavioural therapy then the authors of the editorial should have referred to it. My own reading of the literature is that any specific effect of cognitive behavioural therapy is at best modest and that adequately powered studies are still awaited.

Presenting opinion as substantiated fact might not matter much were it not that such unsupported assertions may be accepted uncritically and used to determine service provision. The editorial seems engineered to support the notion that "during their first episode of schizophrenia young people need specific services"[1] and is in line with the government directive to provide "early intervention teams."[3] The same national plan for the NHS also insists that we provide "assertive outreach teams" and "crisis resolution teams."[3]

The catchment area of 18 000 in the east end of London that I cover in my general adult psychiatry work has none of these services. Nor do I have access to a day hospital, 24 hour staffed care, or any of the other fashionable alternatives to admission that are promulgated. Instead, I work closely with a community mental health team focusing on patients with severe mental illness; none of my patients is currently in hospital. This may not be evidence of anything much; but clinicians should have the right to question whether treatments and service models that are similarly unsupported by evidence should be imposed by central diktat. There are reasoned arguments in favour of the notion that introducing stand-alone teams that deal with only a subset of patients may be unhelpful.

When we are told that we need to provide this or that service in such and such a way we are entitled to ask why. I suspect that often the response we receive would prove unsatisfactory when subjected to even the most cursory examination.

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Authors' reply

EDITOR—Crow says that we failed to cite psychological and drug treatment studies of first episodes of psychosis from the Medical Research Council Centre at Northwick Park. He is right in pointing out that pioneering research in this field took place at Northwick Park in the 1980s. Several more recent studies have broadly confirmed these early findings.

Instead of singling out specific studies we opted to refer readers to a comprehensive review of research in the treatment of first episodes of psychosis.[1] The work done at Northwick Park was in fact included in our editorial. Similarly, with regard to the effectiveness of family therapy in schizophrenia we thought that the meta-analysis that we cited offered better evidence for the efficacy of this approach than any single study on the subject.[2]

Curtis questions the evidence of the efficacy of cognitive behavioural therapy for psychosis in general and our choice of reference in particular.[3] A Cochrane review on this subject concludes that the existing evidence points to additional gains in patients treated with cognitive behavioural therapy plus standard care compared with standard care alone.[4] These gains—in several outcome measures such as relapse rates, global function, and mental state—are in both overall improvement and improvements in specific symptoms such as hallucinations and delusions.[4]

The studies included in the Cochrane review were of patients with chronic schizophrenia. As the focus of our editorial was the treatment of the first episode of schizophrenia we decided that the study by Jackson et al was more appropriate as it concentrated specifically on the effect of cognitive behavioural therapy in the first episode.[3] It is true that in this study the scores for hallucinations and delusions before and after treatment are not reported separately. It is also true that the overall ratings in one of the scales used to measure symptom scores did not differ significantly between patients who received cognitive behavioural therapy and those who did not. However, the group who did receive it showed significant improvements in other symptom measures, had a more positive attitude towards their illness, and had better quality of life.

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Thiazolidinediones for type 2 diabetes

No evidence exists that pioglitazone induces hepatic cytochrome P450 isoform CYP3A4

EDITOR—In their editorial on thiazolidinediones for type 2 diabetes Krentz et al incorrectly stated: "Pioglitazone induces cytochrome P450 isoform CYP3A4, raising the possibility of drug interactions, such as with oral contraceptives."[1] No supporting documentation was provided for this statement.

Ishida et al recently evaluated the relation between the therapeutic effects of troglitazone and pioglitazone in steroid induced diabetes.[2] Urinary excretion of 6β-hydroxycortisol and the ratio of 6β-hydroxycortisol to cortisol were measured as a marker of CYP3A4 induction. Urinary excretion of 6β-hydroxycortisol was significantly increased with treatment with troglitazone but remained unchanged with treatment with pioglitazone.

The elimination half life and plasma concentration of prednisolone were also measured.[2] Treatment with troglitazone significantly reduced the half life and plasma concentration of prednisolone (by about half); no change was seen with pioglitazone. The results of this study indicated that while both drugs were effective in controlling steroid induced hyperglycaemia, pioglitazone

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improved glycaemic control without modification of the steroid metabolism by the liver.

At Takeda Pharmaceuticals we have completed a clinical study (data on file, Takeda Europe, Research and Development Centre) in which we investigated the 6β-hydroxycortisol:free cortisol urinary ratio, commonly used as a specific marker of CYP3A4 induction.[3] Six healthy subjects received pioglitazone 45 mg once daily on day 1 and from day 3 to day 12. Among other variables the 6β-hydroxycortisol:free cortisol ratio in urine was evaluated on day 1 and day 12. The mean (SD) 6β-hydroxycortisol:cortisol ratios in day 1 urine samples (n = 17) and day 12 urine samples (n = 18) were 4.99 (1.92) and 5.11 (2.01) respectively, indicating no difference in the ratio between day 12 and day 1 (P = 0.29). These results clearly show that pioglitazone does not induce the hepatic CYP3A4 enzyme system.

Isoforms contributing to the metabolism of pioglitazone include CYP 2C8 (39%), CYP3A4 (17%), and several other isoforms infrequently used in the known metabolism of other pharmaceutical agents (CYP1A1, CYP1A2, CYP2C9, CYP2C19, and CYP2D6)[4] (data on file, Takeda Pharmaceuticals America). Rosiglitazone is predominantly metabolised by CYP2C8, with CYP2C9 and CYP3A4 contributing to a lesser extent.[5]

In summary, there is no evidence to date that pioglitazone induces the hepatic cytochrome P450 isoform CYP3A4 system.

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Competing interests: Takeda distributes pioglitazone.

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All glitazones may exacerbate heart failure

Editor—We write in response to the editorial by Krentz et al and wish to highlight several issues that need further clarification.[1] Fluid retention is a class effect of the thiazolidinediones (or glitazones).[2 3] All glitazones therefore have the potential to exacerbate heart failure in patients with heart failure. This is not specific to rosiglitazone. The therapeutic indications for the European licence granted to rosiglitazone and pioglitazone are identical.[2 3] These indications do not include combination treatment with insulin for either agent. Additional cardiovascular studies are ongoing for rosiglitazone.

More than 30 publications on rosiglitazone can be found in peer reviewed journals, in particular publications specific to improved glycaemic control in combination treatment as for licensed indications.[4 5]

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Competing interests: SmithKline Beecham distributes rosiglitazone.

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Revised guideline for prescribing vigabatrin in children

Guideline's claim about infantile spasms is not based on appropriate evidence

Editor—The Vigabatrin Paediatric Advisory Group, which in 1998 produced a guideline to "help clinicians when prescribing vigabatrin in children," has now revised it.[1 2] We, the steering committee of the United Kingdom infantile spasm study (UKISS), responded to the original guideline.[3] Our opinion was that there is no evidence that vigabatrin is a better treatment of infantile spasms than hormonal treatments, such as prednisolone and synthetic adrenocorticotrophic hormone preparations.

When we challenged the claim that vigabatrin is the drug of choice, the advisory group offered no rebuttal. Now the claim is stated again, without any appropriate new evidence being produced. Indeed, the finding that visual field losses attributable to vigabatrin occur in children as well as adults strengthens any challenge to the guideline's claim.

We stand by our argument that no one has yet determined the best first line treatment for infantile spasms. To back our challenge we cited the one randomised trial that has compared vigabatrin and adrenocorticotrophic hormone; confidence intervals for this suggest that vigabatrin is unlikely to have a superior treatment effect.[4] Also, we pointed to a lack of studies using neurodevelopmental outcome measures and to new and emerging information about the safety of vigabatrin.

Our desire to gather reliable data is shared by many paediatricians and paediatric neurologists: consultants in over 140 health districts are helping our study to collect evidence about these treatments. Before clinicians can decide if any of the first line treatments for infantile spasms might reasonably be described as the drug of choice they will need to examine (when they become available) the results of studies such as the United Kingdom infantile spasm study.

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1 Appleton RE. Guideline may help in prescribing vigabatrin. *BMJ* 1998;317:1322.
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Advisory group's reply

Editor—Both of Lux et al's letters (this one and that in 1999) have largely, and understandably, promoted the United Kingdom infantile spasm study; their comments have been of little relevance to both the initial[1] and revised[2] pragmatic clinical guideline. At the time that we wrote both guidelines, vigabatrin was the drug of first choice, on the basis of efficacy and safety evidence, in treating infantile spasms; it still remains the drug of choice.

We agree with Lux et al that there is no convincing evidence that vigabatrin shows superior efficacy to adrenocorticotrophic hormone or prednisolone either in controlling spasms or in long term neurodevelopmental outcome. It is disingenuous, though, to ignore the recognised benefits of using vigabatrin in treating infantile spasms–namely, that the drug seems to be effective in at least half of patients[3]; that its effect is rapid (usually less than seven days in patients responsive to vigabatrin[3 4]); and that, unlike adrenocorticotrophic hormone and prednisolone, it does not cause severe side effects.[5] The information currently available on visual field constriction does not alter this opinion, the reasons for which have been discussed recently in more

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detail.[6] With these issues in mind, the justification for the content of the pragmatic guideline should be obvious.

Although we support Lux et al's call for large and well designed comparative studies, methodological and ethical concerns about their study have precluded universal participation in it. Roughly 300 British children develop infantile spasms each year. For these children, their parents and carers, and their clinicians, treatment cannot be deferred pending the findings of the United Kingdom study, whose results will not be available for many years. In addition, because infants who have infantile spasms (and West's syndrome) do not constitute a homogeneous population, the study findings may prove inconclusive. In the interim the guideline simply provides clinicians with pragmatic advice about how and when to use vigabatrin in the paediatric epilepsies, including infantile spasms.[2]

We should emphasise that our opinion is shared by many paediatric neurologists outside the United Kingdom,[3 4 7] including paediatric neurologists in the United States (personal communication).

Vigabatrin Paediatric Advisory Group
Members of the group are: Richard Appleton, consultant paediatric neurologist, Liverpool (to whom correspondence should be addressed at the Roald Dahl EEG Unit, Alder Hey Children's Hospital, Liverpool L12 2AP); Peter Baxter, consultant paediatric neurologist, Sheffield; David Calver, consultant ophthalmologist, London; Celia Cramp, consultant paediatrician, Shrewsbury; John Gibbs, consultant paediatrician, Chester; Graham Harding, consultant clinical neurophysiologist, Birmingham; John Livingston, consultant paediatric neurologist, Leeds; Richard Robinson, consultant paediatric neurologist, London; Isabelle Russell-Eggitt, consultant paediatric ophthalmologist, London; Sheila Wallace, consultant paediatric neurologist, Cardiff; and John Wild, senior lecturer in vision sciences, Birmingham.

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Do tobacco companies encourage young people to smoke?

Accusations against Philip Morris USA are untrue

Editor—Accusations made against Philip Morris USA in both an article and an editorial on candy cigarettes are misleading and untrue.[1 2] The company is categorically opposed to the use of its trademarks on candy cigarettes. Its position on this issue is consistent and clear. The accusations are false and are not supported by the facts.

We do not permit the unauthorised use of our trademarks, including use on clothing or merchandise. We do not authorise others to use our trademarks in ways that we ourselves are prohibited from doing. We continue to take aggressive action, including the filing of lawsuits, to prevent the use of Philip Morris cigarette brand names or logos on any item marketed to minors, such as candy, video games, and toys.

We have taken steps in over 1800 instances to prevent such unauthorised use of our trademarks. Records for the past three decades show that Philip Morris USA has been vigilant in its efforts to prevent trademark violations, especially on products that may appeal to children. Furthermore, in 1990 we began placing paid advertising in trade journals warning other manufacturers that trademark violations will not be tolerated. In 1995 we began to reward those who bring trademark violations to our attention, and this practice continues today.

The documents cited in Klein and St Clair's study—as well as many documents that these authors ignored—support our position that for many years we have fought against companies violating our trademarks, including World Candies. Philip Morris USA would wholeheartedly support legislative action that would prohibit the manufacture of candy cigarettes or other similar products specifically intended to appeal to children. Moreover, the tobacco settlement agreement strictly prohibits the company, and other major tobacco companies, from opposing this type of legislation (master settlement agreement; exhibit F, #8).

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Competing interests: Philip Morris is a global tobacco company.

1 Klein JD, St Clair S. Do candy cigarettes encourage young people to smoke? *BMJ* 2000;321:362-5. (5 August.)
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Philip Morris does market to young people

Editor—Merlo's claim in the letter above (which we had seen at www.bmj.com/cgi/eletters/321/7257/362#EL2) that Philip Morris (PM) does not permit the unauthorised use of trademarks, including use on clothing or merchandise, is untrue. Whenever cigarette companies are asked about this kind of trademark infringement they deny involvement in it and claim that they protect their trademarks and copyrights aggressively. Merlo also claims that since 1995 the company has rewarded those who report violations. Interestingly, she did not comment on the Marlboro look-alike toy mentioned and pictured in Davis's short piece in the *BMJ*'s theme issue on smoking.[1] This "cigarette pack" squirt gun is labelled as "Intended for ages 5 and up."

We have documents from Philip Morris's own files which show that confectioners still had the company's express written permission to use Philip Morris brand names and designs on candy cigarettes at least as late as 1967 (PM 2501003597-98, PM 2501003621-22). (A selection of documents from Philip Morris's files made public through litigation are contained in the Minnesota Tobacco Document Depository, where they are identified by the numbers cited.) In fact, candy cigarettes bearing the legend "made under the license of Philip Morris Inc" were still marketed in 1975 (PM 2501003561-62). Company documents also establish that Philip Morris's permissive attitude toward having its cigarette trade dress appear on children's products did not end even at that late date.

Although Philip Morris had known since at least 1985 that a confectioner was marketing Westernfield candy cigarettes mimicking the Chesterfield brand, it did not obtain a commitment to stop the infringement until 1990 (PM2501003644, PM 2501003349-55). There were several other instances of Philip Morris not bothering to seek even amicable commitments from confectioners until into the 1990s.[2–5]

We would be happy to review other documents establishing Philip Morris's claim if the company were willing to make its complete files available. Otherwise, we are waiting to hear whether Davis has received his award.

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Competing interests: None declared.

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4 Letter from Elzaburu and De Justo from Philip Morris to Especialidades Nadal SA re Marboro and Chesterfold chocolate cigarettes. Jan 14 1991. (PM 2501300804-06.)
5 Letter from Steven C Parrish of Philip Morris to Confetti Fine Confections re sale of Marlboro bubble gum cigarettes. 22 May 1991. (PM 2062100934-35.)

I'm still waiting for my reward

Editor—St Clair and Klein note in the letter above (and at www.bmj.com/cgi/eletters/321/7257/362#EL3) that Merlo has not commented on the Marlboro look-alike squirt gun that I wrote about in the *BMJ*'s theme issue on tobacco.[1] They also wonder whether I have received a reward from Philip Morris, given Merlo's claim that "In 1995 [Philip Morris] began to reward those who bring trademark violations to our attention, and this practice continues today."

Before the *BMJ* published my short piece on the squirt gun along with a photograph of it[1] I brought this toy to the

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attention of tobacco industry lawyers on two occasions. On 2 March 1999, while testifying at a trial in a lawsuit against tobacco companies, I presented the squirt gun to the court. The lawyer representing Philip Morris (Bradley Lerman, of the law firm Winston and Strawn) objected but was overruled by the judge. Lerman then cross examined me about the squirt gun, candy cigarettes resembling tobacco cigarettes, and copyright infringement.[2]

At a deposition on 19 May 2000, in another tobacco lawsuit, I again brought the squirt gun to the attention of tobacco company lawyers. I gave them a photograph of the product (identical to that published in the *BMJ*), and I told them where I bought it. The lawyer representing Philip Morris (Murray Garnick, of the law firm Arnold and Porter) then asked me questions about efforts by the company to protect its trademarks and copyrights.[3]

After bringing the Marlboro look-alike squirt gun to the attention of Philip Morris lawyers in March 1999 and May 2000, and after publishing a short piece about it in the *BMJ*, I am still awaiting my reward from Philip Morris.

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Competing interests: None declared.

1 Davis R. Targeting the kids. *BMJ* 2000;321:354. (5 August.)
2 Testimony of Ronald M Davis in Local 17 International Association of Bridge and Ironworkers Insurance Fund *v* Philip Morris Inc et al, in US District Court, Northern District of Ohio, Eastern Division. Transcript of proceedings, 2 Mar 1999:2233-42.
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What is suspected heart failure with preserved left ventricular systolic function?

Clinical suspicion of diastolic heart failure should rely on more than symptoms of dyspnoea

Editor—Caruana et al's study focuses on the well established difficulties in the diagnosis of diastolic heart failure in the community.[1] I question the authors' conclusions that most patients in the community with a diagnosis of diastolic heart failure have unrelated conditions.

Proposed criteria for the diagnosis of diastolic heart failure require definitive evidence of congestive heart failure by clinical criteria, physical examination, chest radiography, response to diuretics, etc as a starting point.[2 3] The authors do not provide the indications that led the primary physicians to refer the patients for echocardiography; the clinical suspicion of diastolic heart failure should rely on more than symptoms of dyspnoea at rest or on exertion, for which the differential diagnosis is broad.

The authors consider a history of coronary artery disease or electrocardiographic changes consistent with coronary disease to be an alternative explanation for the patients' symptoms. In patients with normal systolic function and without acute ischaemia, physiological stress testing would be mandatory to support this claim; however, no such evaluation was performed.

Lastly, in an elderly population (mean age 71) an E:A ratio of <1.0 is a normal finding and should not be construed as indicating diastolic dysfunction.[4] The use of mitral filling variables in the evaluation of diastolic heart failure is problematic, and it is to be hoped that newer echocardiographic techniques such as tissue Doppler and flow propagation will prove more accurate.[5]

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1 Caruana L, Petrie MC, Davie AP, McMurray JJV. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from "diastolic heart failure" or from misdiagnosis? A prospective descriptive study. [With commentary by A Berger.] *BMJ* 2000;321:215-9. (22 July.)
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Paper does not provide evidence that diastolic dysfunction is a misdiagnosis

Editor—The paper by Caruana et al does not show that patients with suspected heart failure without left ventricular systolic dysfunction are suffering from misdiagnosis rather than diastolic heart failure, as their title implies.[1]

Firstly, the patients studied were from a direct access echocardiography service. Depending on the design of the request form, the referring clinicians may have indicated suspected heart failure for patients with a wide range of pretest probabilities that this was the predominant cause of their symptoms.

Secondly, the mean ejection fraction by Simpson's biplane method was 45%, the cut off point for inclusion in some studies of treatment for systolic heart failure.[2] Furthermore, a quarter of patients had left ventricular hypertrophy, and two thirds had an E:A ratio of <1.0. These are both indicators suggestive of diastolic dysfunction, although no clear cut non-invasive criteria exist for diagnosing this condition.[3]

Thirdly, although obesity and lung disease were identified as non-cardiac explanations for breathlessness, no attempt was made to evaluate their importance in explaining clinical findings. Multiple pathology is common in a breathless population whose mean age is 71, and no comparator group with left ventricular systolic dysfunction was studied.

Caruana et al's paper rightly shows the importance of thorough evaluation to look for multiple causes of breathlessness in this population (including patients with systolic heart failure) but provides no evidence that diastolic dysfunction is a misdiagnosis. We shall not know the relevance of this condition until we have results of treatment studies.

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1 Caruana L, Petrie MC, Davie AP, McMurray JJV. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from "diastolic heart failure" or from misdiagnosis? A prospective descriptive study. [With commentary by A Berger.] *BMJ* 2000;321:215-9. (22 July.)
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Measurement of E:A ratio is both insensitive and non-specific

Editor—We still do not know how often isolated diastolic dysfunction is a cause of heart failure, so Caruana et al's paper was useful.[1] Unfortunately, the authors used only one method of assessing left ventricular diastolic function, the E:A ratio of the transmitral pulsed Doppler signal. This ratio is widely accepted as being both insensitive and non-specific as a measure of heart failure, especially when the authors' threshold of 1.0 is used.[2] Current guidelines use far more stringent criteria for abnormality.[3] In subjects aged over 50 diastolic dysfunction should be considered only if the E:A ratio is <0.5 and associated with an E deceleration time of >280 ms.

A potentially important confounder is the phenomenon of pseudonormalisation, in which an abnormally low E:A ratio reverts to normal as a result of a rise in left ventricular filling pressure. This situation can be unmasked by measuring the A wave deceleration time, the pulmonary vein flow, the pattern of left ventricular flow on colour mapping, or the effect of a Valsalva manoeuvre. None of these methods was used in this study.

In the few trials that have measured ventricular diastolic filling variables in patients with strong clinical evidence of heart failure and normal systolic function, abnormalities have been identified in 20-62% of patients.[4] The clinical importance of such abnormalities may be difficult to judge. If the abnormalities are severe they are likely to be the cause of symptoms. If they are less severe a balanced decision must be made in which other potential causes of symptoms are considered, including obesity, lung disease, and angina (as suggested by Caruana et al). Sometimes a therapeutic trial of a diuretic may be justified. The presence of diastolic abnormalities may explain why some patients relapse after withdrawal of diuretics, especially without echocardiographic control.[5]

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The authors state that "an echocardiogram suggesting diastolic dysfunction on the basis of an abnormal E:A ratio is not diagnostic and represents insufficient investigation." Nobody would disagree with this.

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Author's reply

EDITOR—The E:A ratio may have limitations, as Rimington et al say, but the guidelines that these authors advocate do not help the clinician either. In the same cohort of patients with possible diastolic heart failure the two sets of echocardiographic criteria advocated in the guidelines from the European Working Group on Diastology[1] give a prevalence of diastolic dysfunction varying between 4% (E:A ratio <0.5 and deceleration time >280 ms) and 27%.[2] Clearly, the proportion of patients diagnosed as having diastolic dysfunction will depend on which index is used.

Leibowitz questions our conclusion that most patients with diastolic heart failure have unrelated conditions. Our conclusion was, in fact, that most patients with heart failure and normal systolic function have potential alternative explanations for their symptoms, which they undoubtedly do.

Jay misunderstands our title. We sought to highlight, for non-specialists, the difficulty in diagnosing breathlessness in patients with heart failure and normal systolic function and the limitations of one simple and widely used measure of diastolic function. All we wish to emphasise is that it is important for doctors to resist the temptation to label patients as having diastolic heart failure when an alternative diagnosis may be present. They must also understand that there is, currently, no agreed and reliable echocardiographic measure of diastolic dysfunction.

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1 European Study Group on Diastolic Heart Failure. How to diagnose diastolic heart failure. *Eur Heart J* 1998;19:990-1003.
2 Caruana L, Davie AP, Petrie MC, McMurray JJV. Diagnosing heart failure. *Eur Heart J* 1999;20:393-4.

New drug discovery techniques are not so revolutionary

EDITOR—The optimistic tone of the editorial by Beeley and Berger was surprising.[1] It gave the impression that cascades of new drugs are about to be discovered by the linked techniques of computer aided drug design, combinatorial chemistry, and high throughput screening.

The reality is different.[2] The rate of introduction of new chemical entities to the pharmaceutical market is currently lower than at any time since the second world war. Although these techniques have led to a few successes, in spite of massive investment most companies have failed to generate a single useful lead.[3] One senior executive has expressed the view that the new techniques may be generating bigger haystacks as opposed to more needles.[4] The largest companies are not generating enough novel drugs to sustain them, a fact that has driven the recent spate of mergers. The costs per successful molecule have rocketed. Contrary to the impression given in the editorial, recent historical studies by Healey clearly show that the delay between chemical synthesis and successful marketing was much shorter in the 1950s and 1960s than the most optimistic timescales predicted in the editorial.[5]

The methods dismissed as "archaic" by Beeley and Berger delivered a long series of important therapeutic advances. It will be interesting to see whether the current failures of the new techniques are mere teething troubles or whether they are indicators of fundamental flaws in the understanding of biological complexity.[2]

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1 Beeley N, Berger A. A revolution in drug discovery. *BMJ* 2000;321:581-2. (9 September.)
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Health professionals need more information on vertical transmission of HIV

EDITOR—I agree with Nicoll et al that breast feeding is a significant factor in the vertical transmission of HIV.[1] It is therefore worrying that Whittet et al found that 9% of general practitioners in Lambeth, Southwark and Lewisham responding to a questionnaire thought that breast feeding should be actively encouraged in women who are HIV positive, and 17% did not know what advice to give.[2] It would be interesting to conduct similar research among midwives and health visitors, who are often the main advisers on infant feeding.

Uncertainty on this issue may have been reinforced by the equivocal advice given in a recent *Effective Health Care* bulletin on breast feeding.[3] This bulletin, aimed at decision makers and supposedly evidence based, states: "There is concern at present about the best way of preventing transmission of HIV from mother to baby. International recommendations suggest that women who are HIV positive and who live in communities where there are alternatives to breastfeeding should be advised to feed their babies formula milk. However this removes from these babies the protective effects of breastfeeding against other infections which may be life threatening." The authors go on to refer to a study by Coutsoudis et al, which found that exclusively breastfed babies had similar rates of vertical transmission to formula fed infants and lower rates than partially breastfed babies.[4] However, Coutsoudis has since presented further findings which show that on longer follow up the lowest rates of vertical transmission occurred in exclusively formula fed infants (13th international conference on AIDS, Durban, 9-14 July 2000).

More generally, the debate that has been going on for some time on this issue has been focused largely on developing countries, where the balance of benefits is different from that in the United Kingdom owing to problems with the availability of clean water and adequate supplies of formula as well as high rates of life threatening infections other than HIV. In the United Kingdom all babies at risk of vertical transmission of HIV potentially have access to safe formula feeding. Current evidence in this situation supports exclusive formula feeding in women who are HIV positive. The evidence presented by Whittet et al[2] suggests that unequivocal advice, based on the situation in the United Kingdom, should be made available to all health professionals who are in a position to inform and advise this group of women.

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1 Nicoll A, Newell M-L, Peckham CS. Breast feeding is a major factor in HIV transmission. *BMJ* 2000;321:963. (14 October.)
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