Letters

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Follow up care in general practice of patients with myocardial infarction and angina

Trial was underpowered

EDITOR—The paper reporting the trial to improve follow up in general practice of patients with coronary heart disease after discharge from hospital is unduly pessimistic.[1] At least one of the authors (Mant) has been in this situation before.

Mant worked on the OXCHECK study, which found comparable differences of less than 5% between control and intervention groups and in which a strategy identifying patients at high risk was abandoned in favour of targeting those with established disease at yet higher risk.[2] It was left to Field et al to show that the OXCHECK study was successful and that the incremental addition of assessment of multiple risk factors to a pre-existing programme targeting smoking and blood pressure was a cost effective way of improving risk factors.[3 4]

The failure to show substantial differences in outcomes in both Jolly et al's trial and the OXCHECK study has resulted from flaws in the expectations and design of both trials. The trials are based on a prior assumption of the size of the effect of the intervention that is greater than that repeatedly found in similar trials aiming to improve professional organisation and behaviour—pragmatic trials testing well organised delivery versus less well organised delivery.

It is unlikely that any trial would be feasible to show improvements in aspirin prophylaxis or outcomes among practices already reaching 80% of the target population. Both trials were underpowered to detect differences in physiological outcomes of 1-5%, which might more realistically have been predicted to result from improvements in prescribing or advice of the order of 2-6%.[1 2]

What are the minimum outcome differences considered cost effective, and how large would the trial need to be and for how long would it need to be sustained to show these? These assumptions need to be considered within an incremental framework, as doing nothing is not a realistic option. Will these underpowered trials persuade anyone to invest in larger, better designed studies, or will we go on running trials designed to fail because of unrealistic prior assumptions?

Improvements in professional organisation yield marginal though important benefits. Given the effort and commitment required to mount even a small study of this kind, time and pretrial modelling might usefully be spent in clarifying the smallest difference worth investing in and the feasibility of mounting a trial sufficiently large to test these small but important differences. Jolly et al's study confirms that improvements in delivery do not in the short term yield large changes in risk factors but do consistently yield small, important, improvements—a conclusion that the multiple risk factor intervention trial reached 20 years ago.[5]

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1 Jolly K, Bradley F, Sharp S, Smith H, Thompson A, Kinmonth AK, et al for the SHIP Collaborative Group. Randomised controlled trial of follow up care in general practice of patients with myocardial infarction and angina: final results of the Southampton heart integrated care project (SHIP). *BMJ* 1999;318:706-11. (13 March.)
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Author's reply

EDITOR—When colleagues and I designed the OXCHECK trial we had already confirmed that brief advice in general practice could increase smoking cessation rates.[1] Our studies of dietary advice were less consistent but seemed to show that a well structured and supported intervention could achieve a reduction in serum cholesterol concentration of up to 5% in selected patients.[2] Our interpretation of the results of the OXCHECK trial was in the context of the greater effectiveness of these interventions regarding single risk factors. It was also in the context of our experience that the likelihood of an invitation to attend being accepted was inversely related to cardiovascular risk.[3]

Contrary to Robson's assertion, the OXCHECK trial was not underpowered; the difference in serum cholesterol of 2.3% was significant, and the precision of the estimate of the difference in smoking cessation rates was high (95% confidence interval −3.5 to 1.7%). We concluded that the public health importance of the difference in cholesterol concentration depended on the time for which it was sustained. Again, this reflected existing knowledge that the additional benefit of individual advice on lifestyle over community education is lost over a relatively short period.[4]

The situation in the SHIP trial was in some ways similar. We started with the knowledge that both exercise rehabilitation and appropriate drug treatment can substantially reduce morbidity and mortality. We also had evidence that these interventions were not being implemented effectively in everyday practice in the trial area.

The SHIP trial had less power than the OXCHECK study to detect physiological change (95% confidence interval for difference in total cholesterol −0.33 to 0.06 mmol/l), but the anticipated effect included increasing attendance for exercise rehabilitation and adherence to drug treatment—both of which are associated with a much larger effect size than lifestyle interventions. Moreover, we incorporated a qualitative study within the SHIP trial's design and measured intermediate process outcome measures so that we could gain information to improve the quality of NHS care whatever the physiological outcome.[5]

The cost effectiveness of care needs to be measured against alternative ways of providing that care and must take account of opportunity costs. Showing absolute marginal benefit is not enough. In 1990 we concluded that doctors should be careful not to absolve the government of its public health obligations by substituting unproved preventive interventions aimed at individual patients.[3] I still believe that this is true.

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Assessment of mother and fetus in labour

Article is not evidence based

EDITOR—In its advice for authors[1] of ABCs the *BMJ* states that "there are now many … good systematic reviews" and that "we would like … evidence for key statements." But is this advice always followed?

My concern was raised by Steer's article on assessment of the mother and fetus in labour in the ABC of labour care, in which electronic fetal heart rate monitoring is discussed.[2] No systematic reviews are listed in the key references. The systematic reviews published by the Cochrane Collaboration show no apparent benefit in terms of neonatal outcome.[3 4] This is not mentioned in the ABC; rather it is stated that electronic fetal heart rate monitoring has had a "bad press," and it is suggested that this could be due "to a false expectation that it could reveal all about fetal condition during labour." A more straightforward explanation might be that it adds no benefits beyond intermittent auscultation but is expensive, increases the risk of caesarean section, and promotes a false need for centralisation of births.

More specifically, a box lists some "accepted indications for continuous electronic fetal heart rate monitoring in labour," including labour before 34 weeks. It is not clear why and by whom these indications are accepted. The inclusion of this indication is especially odd as a trial that focused on premature infants showed a large and significant increase in cerebral palsy (relative risk 2.5) among babies monitored electronically, and no benefits.[5] Is the list of indications exclusively opinion based and sometimes contrary to firm evidence or does some evidence exist to support it? If it is opinion based I suggest that the table of accepted indications is revised before the ABC of Labour Care is published as a book and that thorough explanations are given if any of the advice is against firm evidence.

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Author's reply

EDITOR—I could have understood Olsen's concern if I had recommended continuous electronic fetal heart rate monitoring in my article. In fact, I was careful not to do so. Most maternity units use continuous monitoring, at least for women they consider to be at high risk. I therefore thought it important to describe current practice. I could have discussed the pros and cons of continuous monitoring in detail but thought that there was insufficient space in an ABC article to do this properly.

Readers who want a detailed discussion (with 339 references) can refer to my latest book chapter on the topic, which I wrote with Danielian.[1] The chapter refers to the Cochrane database as does Olsen, but in the 1999 version the most recent meta-analysis of nine randomised controlled trials showed a significant reduction in the incidence of neonatal seizures associated with the use of continuous electronic monitoring (relative risk 0.5 (95% confidence interval 0.30 to 0.82)).[2] The same authors emphasised this finding in another meta-analysis, including three further studies.[3]

Vintzileos et al also reviewed nine trials and pointed out that if the analysis was confined to deaths attributed to hypoxia there was a significant reduction in perinatal mortality (odds ratio 0.41 (0.17 to 0.98); 0.7 *v* 1.8/1000) associated with the use of continuous monitoring.[4] I was careful in my review to point out that continuous monitoring should be used only as a screening test—specifically for umbilical cord compression, hypoxia, and acidosis—and then only if supplemented by fetal blood sampling with pH measurement; the best way to screen for fetal acidosis is to search for babies with a low pH. I emphasised that continuous monitoring could be misleading in other conditions, such as infection.

The indications for continuous monitoring were taken from a list suggested by Neilson in an editorial in the *BMJ* in 1993.[5] Interestingly, Neilson is a senior editor for the Cochrane collaboration. In my experience his views are representative of current opinion and practice.

In relation to Shy et al's trial focusing on preterm infants, Olsen fails to mention that in the continuously monitored group some labours were allowed to continue for hours despite an abnormal heart rate pattern, and the association between the duration of abnormality and the subsequent development of cerebral palsy was highly significant.

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1 Steer PJ, Danielian PJ. Fetal distress in labor. In: James DK, Steer PJ, Weiner CP, Gonik B, eds. *High risk pregnancy-management options*. London: WB Saunders, 1999:1121-49.
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Labour care of women with HIV infection

Article did not highlight current guidelines

EDITOR—In the section on women with HIV infection in their article for the ABC of labour care, Chamberlain and Steer make several controversial and unreferenced statements.[1] The key message recognises the importance of screening pregnant women for HIV infection to enable appropriate care to protect the baby; it makes no mention, however, of maternal health, preferring to highlight staff protection. In obstetrics and midwifery it would be preferable to emphasise the need to practise universal precautions to protect against any transmissible infections rather than selective practice, which puts staff and patients at risk and may stigmatise women with HIV or other infections.

The authors state that "women known to be HIV positive should be taking zidovudine and protease inhibitors during the second half of pregnancy." The British HIV Association has written guidelines on prescribing for HIV infection in pregnancy and recommends triple antiretroviral therapy (usually zidovudine, another nucleoside analogue, and either a protease inhibitor or a non-nucleoside reverse transcription inhibitor) after the first trimester for women who, if they were not pregnant, would normally be advised to take antiretroviral therapy for their own health. For women who are asymptomatic with high CD4+ lymphocyte counts and low HIV plasma load monotherapy with zidovudine from the start of the third trimester plus caesarean section before labour begins is an option.[2] Avoidance of breast feeding, zidovudine monotherapy, and elective caesarean section reduce transmission to below 2%.[3 4]

We are not aware of any trials of two protease inhibitors in pregnancy. In a recent study monotherapy with ritonavir reduced transmission from 19% to 9% (a similar efficacy to zidovudine) when given from week 36 of gestation. Ten of 74 women, however, stopped treatment because of side effects.[5] Prescribing of antiretroviral drugs is rapidly evolving, and the management of pregnant women should be undertaken in liaison with experienced HIV physicians. The safety of antiretroviral therapy in pregnancy remains unproved, and all mother-infant pairs should be reported to the schemes set up by the Royal College of Obstetricians and Gynaecologists and the Royal College of Paediatrics and Child Health.

The protective effect of caesarean section is seen only when the section is carried out before labour, which suggests that avoiding labour is important.[3 4] The 50% reduction in transmission with caesarean section documented in the European randomised mode of delivery study was with standard operating techniques.[4] Any additional merits of using a staple gun to make the lower uterine segment incision are presumably speculative, and an unachievably large clinical trial would be required to show any reduction in transmission.

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Authors' reply

EDITOR—We fear that Taylor et al have misunderstood the remit of the ABC series, which is to provide a brief overview for generalists. We therefore wrote our ABC in a general way, not laying down specific guidelines, which change with time. We wonder if the guidelines that Taylor et al now recommend will be the same in a few months.

We were strictly limited by the *BMJ*'s editors to a few references per article, and of necessity some of our statements were unreferenced. We agree that universal precautions against infection are preferable and recommend them in our own units. We find, however, that despite our exhortations, many staff (especially juniors) fail to observe them unless they know that a patient is definitely HIV positive. We think it is unlikely that staff are more vigilant in places where the incidence of HIV infection is low. Realistically, therefore, knowledge of HIV status is unlikely to be available everywhere to prompt staff to take proper precautions against infection.

We used the plural for protease inhibitors to indicate that there is more than one that might be used. It is appropriate for Taylor et al to publicise the recommendations they have made, but we would point out that they come from a meeting that took place after our article was written. We deliberately avoided being too precise or prescriptive so as to make clear that this is a rapidly changing area, in which recommendations change frequently. We consider that it should be dealt with only by specialists active in the latest developments.

To avoid exposing the baby to maternal blood it seems sensible to take any precautions at caesarean section to achieve this, including using staples where these can be shown to produce a more bloodless field. We realise that this technique has never been the subject of a randomised clinical trial—but neither has tying one's shoelaces, yet this is still recommended to anyone wishing to walk safely.

When the next edition of the *ABC of Labour Care* is published we will incorporate information about whatever regimens are then recommended practice.

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Report on future of prison health care will lead to progress in improving this care

EDITOR—In an editorial Smith draws attention to a report on the future organisation of prison health care.[1 2] He correctly summarises the report's findings, but we would make several comments.

The report considered a range of organisational options, including full transfer of prison health care to the NHS. For important reasons, however, this would not be practical in the short term. Firstly, both the NHS and the prison service are implementing radical programmes of change and must consider the implications of this for prison health. Secondly, while prison healthcare staff are currently isolated from the NHS, transfer of responsibility would run the risk of introducing new dividing lines, isolating healthcare staff from the prison service and creating new perverse incentives. Thirdly, health is not just about health care. A healthy prison regime will have a considerable effect on health and requires the full involvement of the prison service. Finally, arrangements for prison health care must not undermine the role of the prison governor as the person responsible for running the prison. The working group concluded that prison health could be delivered only by the NHS and prison service working in partnership.

In its response to the report the government gave a commitment to proposals aimed at providing health care for prisoners equivalent to that provided to the general population. Prisons and health authorities will be asked to work together to assess prisoners' health needs and to plan service delivery. They will be supported in their joint working by a task force. A prison health policy unit will be established to provide a strategic direction for prison health. Smith comments that it has not been decided where this unit should be. The government announcement clearly stated that it would be in the Department of Health. This underlines the new commitment to partnership and will ensure that prison health policy draws on and develops in line with wider national health policies.

These are important initiatives, and we can now begin to make progress in improving health care for prisoners. The response to the report from both prison service and NHS staff working with prisoners suggests that we will have much support in pursuing this challenging agenda.

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Managing osteoporosis in older people with fractures

Many figures in editorial were overstated

EDITOR—Articles that raise the profile of osteoporosis should not lead to overreactions by exaggerating both the consequences of the condition and the effectiveness of preventive methods. Doube's editorial on osteoporosis in elderly people unfortunately does this.[1]

This is a difficult condition on which to put precise figures for mortality and morbidity as many of the outcomes are related to other conditions customarily present in this population. The aetiology of a hip fracture is related to the processes of ageing, including impaired mobility, vision, and neuromuscular coordination. To attribute all subsequent deterioration to the fracture is inappropriate. The mortality of 33% quoted by Doube relates to the mortality at one year,[2] and all deaths over

this period should not be attributed to the hip fracture. About 10% of deaths will be expected in this elderly population over one year and a further 10% can be accounted for by associated medical conditions, which leaves a more realistic mortality figure of about 10%.[3] The figure of 33% of the surviving patients requiring institutional care is also exaggerated; a more realistic figure of around 10% is appropriate.[2]

The quoted effectiveness of preventive measures should not be overestimated. Doube states that vitamin D analogues will reduce the fracture rate by 50%. This is at variance with the Cochrane review on vitamin D analogues, which states that "uncertainty remains about the efficacy of vitamin D" and recommends further randomised trials on this question.[4]

Unquestionably, we need to direct more attention to reducing the number of osteoporotic fractures. Any measure undertaken must be based on good quality evidence, which is currently not available. We need to define who needs treatment, what treatment should be used and for how long, and how effective this treatment is. Let us set about getting these answers before we recommend what may be ineffective interventions.

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Patients should be given written advice about lifestyle

EDITOR—Doube's editorial is about managing osteoporosis in older people with fractures.[1] We report here our experience with patients receiving long term systemic steroids.

Identifying patients at risk of osteoporotic fractures is crucial since intervention can be made early. As part of their management, patients receiving long term systemic steroids should be given lifestyle advice aiming at bone preservation (for example, limitation of alcohol and cigarette consumption, adequate calcium intake, regular weight-bearing exercise).[2] At North West Hertfordshire, guidelines are available on the diagnosis and management of osteoporosis induced by corticosteroids. It is recommended that all patients taking long term systemic steroids should receive lifestyle advice. Dual energy *x* ray absorptiometry is recommended, and intervention advised according to the results of the scans.

We carried out an audit at our hospital between October 1998 and January 1999. Patients who had been taking oral steroids for six months or more were recruited from the medical wards and the respiratory outpatient clinics. Patients were asked whether they had received lifestyle advice and whether dual energy *x* ray absorptiometry had been performed. Results of the scans and treatment given to patients were sought.

Altogether 57 patients (31 male) were recruited (median age 64). The median duration of steroid treatment was 48 (range 6-480) months. The median dose of steroids at the time of interview was 10 (range 2.5-40) mg. All patients were taking prednisolone. Only five patients could recall having received lifestyle advice. Twenty six patients had had dual energy *x* ray absorptiometry (within three years of interview): nine had normal scans; nine had osteopenia at one site or more (no osteoporosis); and eight had osteoporosis at one site or more. All patients with osteoporosis received treatment.

Our finding that few patients taking long term systemic steroids could recall having received lifestyle advice may be common elsewhere. We suggest that written advice about lifestyle should be given to these patients at the start of their treatment. The small proportion of patients taking oral steroids who had dual energy *x* ray absorptiometry may be related to poor awareness of agreed guidelines by staff involved in the care of these patients. This needs to be rectified.

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Radiosurgery for brain tumours

EDITOR—Brada and Cruickshank express their concerns about the lack of evidence based research in the field of radiosurgery.[1] We agree that radiosurgery replaced neurosurgical resection or fractionated radiotherapy in the treatment of certain intracranial lesions before randomised controlled trials were performed.[2–5] However, the original and continual biological basis for radiosurgery remains strong. The early pioneers in radiosurgery understood that once irradiated volumes could be reduced dramatically the need for fractionation became less important. It was also understood that large single doses of radiation were particularly damaging to late responding tissues, explaining why obliteration rates for arteriovenous malformation treated with radiosurgery were substantially higher than those seen rarely after fractionated radiotherapy. Twenty year follow up does now exist for patients treated with radiosurgery for acoustic neuromas, arteriovenous malformations (at Karolinska Hospital[4]), and pituitary adenomas (at Massachusetts General Hospital), and the results strongly support its continued use for the future. Recent results of patient assessments for quality of life outcomes suggest that patients are more satisfied with the outcome from radiosurgery compared with other therapeutic modalities.[2]

It is ironic that this editorial immediately preceded the fourth congress of the International Stereotactic Radiosurgery Society. This congress was the largest ever and was attended by over 400 neurosurgeons, radiation oncologists, and physicists worldwide. The founders of the society set out more than eight years ago to create a scientifically based group of clinical investigators so that results could be presented in a critical fashion to other members. Rather than publishing a skewed view of the current state of radiosurgery, we would encourage the authors of the editorial to participate in the design of important prospective trials to address their concerns.

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Autoinflation for treatment of glue ear

Autoinflation does not produce worthwhile benefit

EDITOR—A review of nasal balloons is welcome, given the high prevalence of glue ear (otitis media with effusion) and the devices' simplicity.[1] The authors conclude from three studies that the balloon may be of benefit. The two published studies to which they refer merit closer attention.[2 3] The studies suggest short term benefit, but it is not sustained. No significant differences could be found in either study between treated and control groups in tympanometric resolution at two or three months' follow up. Compliance was poor in over half the children and got worse with time. Any benefit is lost after treatment is stopped.

Reidpath et al have included the two-week outcomes in one trial[2] and the 12-week outcomes in the two others (Blanshard et al[3] and the unpublished data), even though benefit decreases significantly with time, biasing the results in favour of the treatment. The greater prevalence of type B tympanometry in one untreated group[3] is an additional source of bias, as is the lack of blinding and adequate randomisation in any study. The

result is the conclusion that the treatment is effective, with an odds ratio of 3.5. Meta-analysis of poor research gives poor answers.

Reducing all the information in a paper to a single odds ratio can be a powerful tool but also hides much of the available information. Meta-analysis is not the best way to analyse three small studies of variable methodology. The conclusion is the inevitable refrain that "more/bigger/better studies are needed." In his commentary on the paper Haggard mentions the need to prioritise research endeavour to maximise payback.[1] Surely it is wrong to recommend that large, expensive, time consuming studies be done on an issue for which the answer is already available. The nasal balloon produces no sustained benefit in glue ear, and after three months' watchful waiting no large difference can be expected in the number of children requiring surgery. This is the real issue.

Haggard mentions that nasal balloons may have a place as a temporising measure. Is he suggesting that although the device produces no worthwhile benefit, we can use it as a placebo while nature takes its course? This would be deception of the worst kind, since the balloon is not available on prescription in the United Kingdom and must be paid for by parents. Glue ear is associated with social deprivation, and we must not ask our poorest patients to pay for a worthless device simply to keep them amused.

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Authors' reply

EDITOR—The rapid responses to our review of trials of autoinflation for glue ear (http://www.bmj.com/cgi/content/full/318/7192/1177#responses) would suggest that we are damned if we do and damned if we don't (recommend autoinflation). Of the five rapid responses, Kubba's (printed here) suggests that autoinflation is worthless and would not support further trials; two (those from Willis and Tostevin) clearly support current use of autoinflation ("to discontinue the use of nasal balloons may deny a group of patients access to a non-invasive, non-surgical management option"); and two (those from Temmel and McKenzie) make useful suggestions about the trial's design. Such equipoise is the ethical prerequisite for a randomised trial.

Kubba suggests that benefits may be only short term. Even if this proves to be so, it may be useful given the dynamic nature of middle ear effusions: in a monitoring study of the natural course of otitis media with effusion Hogan et al suggested a mean duration of unilateral effusion episodes of 5-6 weeks.[1]

We agree with Kubba that the quality of current trials is poor, but we interpret this to mean that better research rather than no research would be the best option. Paradise suggests that in the United States children younger than age 3 undergo an estimated 313 000 grommet operations a year, at a cost of about $750m (£500m).[2] Given the current variation in the use of autoinflation, wouldn't it be worthwhile investing a small portion of the millions spent on current treatment for properly testing simple interventions such as autoinflation? We believe that this makes good sense both clinically and economically.

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Evidence based budgeting is now necessary

EDITOR—The *BMJ*'s occasional notes on economics will certainly enlighten physicians on important aspects of health economics. As Palmer and Torgerson mention, the application of economic analyses remains a challenge to decision makers everywhere.[1] Although the efficiencies covered in the note are invaluable as starting points for the allocation of resources, it sometimes seems that the decision making is made easier by the application of two other global measures of efficiency—political efficiency and putatively pragmatic efficiency.

Political efficiency might be defined as allocation of healthcare resources to the maximum political advantage of those in charge of the purse strings. Indeed, the intervention under consideration need not be efficient by any other criteria. A recent example in Canada was the announcement that the Canadian Blood Service will spend $C20m (£8.9m) annually for genome amplification testing to allow earlier detection of the viruses that cause hepatitis C and AIDS. It is estimated that genome amplification testing will identify an additional five to seven cases of hepatitis C infection among blood donors each year and an additional case of HIV infection every two to three years. This converts to spending $C2.9m-4.0m (£1.3m-1.8m) per case of potential hepatitis C infection and $C40m-60m (£17.8m-26.6m) per case of potential HIV infection identified.

The converse is putatively pragmatic efficiency. In this it is implied that, usually because of hospital budgetary constraints, there are insufficient resources to apply to a new, and generally more expensive, intervention even if it has been shown to be effective, and maybe even cost effective, according to recognised criteria. The intervention might well be efficient in other ways if applied within the community of the hospital. How resources are allocated from within the hospital budget is not obvious to most clinicians. Or they may get a glimpse of their own piece of the pie but not have a sense of how big the pie really is or how and on what basis it is being divided.

Evidence based medicine is all the rage; if an expensive intervention is shown to be worthwhile, strong leadership will be needed to ensure the appropriate evidence based budgeting.

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1 Palmer S, Torgerson DJ. Economics notes: Definitions of efficiency. *BMJ* 1999;318:1136. (24 April.)

Stories in TV drama series about psychiatry were researched in detail

EDITOR—Persaud complains that Channel 4's drama series *Psychos* "does not hit a realistic note"; he goes on to comment that "the respect accorded to the senior doctors made me wonder where in the NHS the series had been researched."[1] As a psychiatric "consultant" to *Psychos* I know that the writer of the series shadowed several psychiatrists, including one working in Persaud's own unit. Perhaps Persaud was away at the time making his own contribution to quality television on ITV's midday show *Richard and Judy*.

Persaud finds himself "intrigued that no users of mental health services were consulted for the series"; they were, frequently. He goes on to complain that "none of the psychiatrists in the series is the least bit likeable" and, as a solution, suggests that "script writers and programme makers should be more closely supervised by their psychiatric consultants." To my mind this suggests a misunderstanding both of the television drama genre and of the role of the professional adviser in the making of a television programme.

A television drama series must be dramatic if it is to attract viewers. *Psychos* makes for compulsive viewing, is a gripping drama, and from a programme maker's perspective is a run-away success. The psychiatric consultants employed by the production company have done their job by ensuring that the storylines fall within the bounds of possibility and that technical details such as the indications for and doses of particular drugs are accurate.

As a doctor I welcome programmes that "portray the practice of medicine" and "show how treatments actually work"; I recognise, however, that this is not the job of

a fictional drama series. Perhaps the success of *Psychos* will encourage programme makers to produce a psychiatric documentary designed to inform rather than entertain. I trust that such a programme would be more to Persaud's taste.

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1 Persaud R. Doctors taking over the asylum. *BMJ* 1999;318:1360. (15 May.)

Sex difference in prescription of asthma drugs is smaller than previously found

Editor—We were surprised to see the relation between people's sex and, in those with asthma, their likelihood of being prescribed oral steroids, as found by Sexton et al.[1] We analysed a larger dataset, as they suggest. We included computerised 1996 RNZCGP data from a consulting population of 201 954 patients (90 214 men and 109 079 women; 2661 sex not recorded). The nature and reliability of the RNZCGP database are well established.[2 3] The target patients were in the age band 20-54 years (42 264 men and 55 670 women). Patients were identified as asthmatic if they received a prescription for inhaled corticosteroids, inhaled β agonists, inhaled sodium cromoglycate or nedocromil, or theophylline (table).

In our dataset, the raw odds ratio of receiving a prescription for oral corticosteroids is 1.39 (95% confidence interval 1.17-1.65) for women compared with men. This is significant but may have minor clinical importance. Logistic regression analysis of our data using sex and the number of asthma consultations as explanatory variables found the odds ratio for oral steroid use for women compared with men almost identical to 1.39 after controlling for the number of asthma consultations. This is because the increase in the proportion of patients taking oral steroids with a number of asthma consultations is similar for men and women, which contrasts with the dose response data of Sexton et al. The proportions prescribed oral steroids more than once were 120/2961 (4%) of women and 47/1922 (2.4%) of men, which is also significant.

The proportion of women with asthma who received at least one prescription for oral corticosteroids is less by a factor of more than two than that found in the study by Sexton et al. The sex odds ratio we found for prescriptions of oral corticosteroids is substantially lower (1.39 *v* 5.55). This difference could perhaps be related to the selection criteria employed by Sexton et al, with only questionnaire responders being included, or to our differing definitions of asthma. Of 253 patients possibly asthmatic on the basis of prescribing alone, only 16 were considered not asthmatic for the Sexton analyses. We therefore do not consider the different inclusion criteria for our own much larger analysis cohort to be crucial to the rather different results. We are unable satisfactorily to address actual dispensing or drug use from our computerised data. There may be other confounding factors. Overall our data support the view that if the difference in the rate of prescribing oral corticosteroids to women compared with men is not due to confounding, it is likely to be of lesser magnitude than described by Sexton et al.

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Numbers (percentages) of men and women prescribed asthma drugs (following Sexton et al[1])

	Additional drugs		
		Corticosteroids	
	β Agonist	Inhaled	Oral
Women (n=2961)			
Total*	2444 (83)	1636 (55)	442 (15)
β Agonist and	1113 (38)†	1210 (41)	388 (13)
Inhaled steroid and	–	–	313 (11)
Inhaled steroid and β agonist and	–	–	267 (9)
Men (n=1922)			
Total*	1623(84)	1031 (54)	216 (11)
β Agonist and	768 (40)†	795 (41)	191 (10)
Inhaled steroid and	–	–	153 (8)
Inhaled steroid and β agonist and	–	–	131 (7)

*The three treatments are not mutually exclusive. 445 (9.1%) of patients were prescribed other asthma drugs such as theophylline. †β Agonist only.

Some patients with colorectal cancer may have been missed by Northern Ireland registry

Editor—The number of new patients with colorectal cancer (3217 over a five year period) given by Kee et al[1] would give a crude incidence of colorectal cancer in Northern Ireland of 39.5 per 100 000 people. As their study included only patients having surgery, however, correction needs to be made for this. Although population rates of surgery for colorectal cancer are not widely published, the range seems to be narrow in the United Kingdom and Ireland—typically from 80% to 85% of all incident cases.[2–4] The rate of histological verification of diagnosis in Northern Ireland, at 87%, was typical for United Kingdom and Irish registries, and so rates of surgery can be assumed to be consistent with the other published data.

Using rates of surgical intervention from 80% to 85%, the overall incidence for Northern Ireland would be estimated, from the data of Kee et al, to be between 46.6 and 50.3 per 100 000 people per year. This is considerably lower than the population based incidence estimates for Northern Ireland for 1993-5 (57.2 per 100 000).[5]

The discrepancy in incidence raises the possibility that some patients have been missed by the colorectal cancer registry. As all hospitals may not have been equally assiduous in reporting cases to that registry, survival data from some centres may be biased. Caution is needed in interpreting data on survival from hospital based registration, and comparison of survival between hospitals should be based, where possible, on cases from a comprehensive population based registry.

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Rating information on the internet can empower users to make informed decisions

Editor—Last year Diepgen and I proposed rating information on the internet with a standard vocabulary of machine-readable metadata.[1] In his comment on our paper Whatling incorrectly implied that we intend to "dismiss the input of non-medical readers."[2] This is a misunderstanding—we merely aim to empower users to make informed decisions.

I would not call the efforts of physicians to evaluate information on the internet

"arrogant." Using that argument, it would be arrogant for peer reviewers for scientific journals to assess submitted papers or for a doctor to give health advice to patients in daily practice. We argue that physicians have the duty to guide patients through the information jungle. This can be done by evaluating printouts from the internet that puzzled patients bring with them. A smarter way, though, would be to distribute such evaluations on the internet, using an infrastructure such as medPICS.[1 3]

Whatling's notion that everything on the internet can be falsified is incorrect. Raters of our med-CERTAIN project will be able to use digital signature labels, which allow end users to check the authenticity and integrity of ratings.[3]

Lastly, Whatling's assertion that "patients have read and heard numerous reports of magical cures and cancer healers for hundreds if not thousands of years in one form or another and have given these the short shrift they deserve" is not supported by scientific evidence.[4] Besides, to extrapolate from early times, when people did not have books, to the emergence of the internet—the most profound change in communication since Gutenberg's inventions—and to predict that these developments have no effect on how people understand and digest information is absurd. McLuhan coined the aphorism "The medium is the message," arguing that any new medium will impose a new environment and that the modes of disseminating data will cause culture changes, including the way we see, deal with, and assess the things around us: "We shape our tools and they in turn shape us."[5]

The internet is the world's largest library, shopping mall, business market, museum, university, health information provider, and entertainment vehicle. It facilitates the sharing of ideas, data, and tools, creating an ethos of cooperation and collaboration; has the potential to empower patients and to bring evidence into medical practice; but also creates an environment of chaos and information overload. Both sides have to be kept in mind and all possible measures should be evaluated to push the balance towards the beneficial effects.

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Mortality associated with oral contraceptive use

Confounding might have accounted for results

Editor—Beral et al have reported an increased relative risk of death from cervical cancer among women using oral contraception.[1] Their study controlled for smoking but not for the other principal risk factors for cervical cancer, which include infection with human papillomavirus of a high risk type, sexual behaviour, and inadequate cervical screening. There is therefore a considerable risk of confounding, which could account for the results.

The authors do not give patterns of use of contraception by never users and non-users of oral contraceptives; it would be interesting to know what proportion of this comparison group was using barrier methods. Such women are at reduced risk of cervical cancer,[2] and therefore a comparison that includes a large proportion of women using barrier methods will seem, artificially, to increase any risk in pill users.

It should also be noted that durations of use of less than 10 years are not associated with a significant increase in risk in this study. This apparent duration of use effect may well be related to the risk of acquiring an infection with an oncogenic human papillomavirus.

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Relative risk of liver cancer remains high

Editor—Beral et al state that, for ever users of oral contraceptives compared with never users, both the overall relative risk of death and the relative risk of death from all cancers are 1.0.[1] They discuss the fact that the relative risk of cervical cancer is 1.7 but ignore the relative risk of liver cancer, which is 5.0. After ≥20 years since first use of oral contraceptives, liver disease still has a relative risk of 1.8—on an equal footing with cervical cancer—although no separate breakdown is shown for liver cancer. In the table of data for last use of oral contraceptives ≥10 years previously, liver disease scores a high relative risk; again liver cancer is not shown.

It is important that the not so comfortable outcomes do not get lost among the good outcomes in the final message to end users.

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Authors generalise their results to cohort that was never studied

Editor—In their paper on mortality associated with oral contraceptive use Beral et al write: "There is little to suggest any persistent adverse effect 10 or more years after use of oral contraceptive ceases."[1] This conclusion is probably invalid because the authors generalise their results to a cohort that was never studied.

Beral et al recruited 23 000 women in the late 1960s. But women took oral contraceptives in a far different manner in the 1960s than in the later 1970s, 1980s, and 1990s. Women took them for longer periods earlier in their reproductive lives in the 1980s and 1990s than in the 1960s and 1970s, as was noted in a large Oxford meta-analysis published in 1996.[2] For example, the meta-analysis noted that in women under age 35, 42% took oral contraceptives before age 20 and 2% took them after age 30. In contrast, in women aged 45-54, many of whom would have taken oral contraceptives in the 1960s (as the women in Beral et al's study did) only 1% took them before age 20 and 54% after age 30. Beral et al were, essentially, studying a cohort of women who often took the pill after having at least one baby. Their results cannot be applied to the millions of women who take oral contraceptives before first term pregnancy and who often do so for years before having a child.

This is critical because breast cells are most vulnerable to carcinogens before a woman has a baby. Russo and Russo noted this in their extensive work in the rat model.[3] Rats were given the carcinogen dimethylbenzanthracene; 69% of virgin rats developed breast cancer but none of the rats that were allowed to complete their pregnancy did so. In humans the same phenomenon is observed.

Women who have children have less breast cancer than those who do not have children, and women who have children at an earlier age have a lower risk than women who have them later. In addition, women who are exposed to radiation before having a child are at far higher risk of developing breast cancer than those who are exposed after giving birth.[4]

Finally, in a meta-analysis in 1990 Romieu et al noted that women who used oral contraceptives for four years or more before first term pregnancy had a 72% increased risk of developing breast cancer.[5] Even the Oxford meta-analysis[2] had no table or analysis of this important cohort (women who take the pill before first term pregnancy).

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Medical profession needs to examine facts

EDITOR—The Royal College of General Practitioners' study of mortality associated with use of oral contraceptives is interpreted in the media as "giving the pill the all clear."[1] Risks for current users are not given, but ever users have significantly increased relative risk of death from cerebrovascular disease (1.5) and accidents and violence (1.6). The relative risk of liver cancer was 5.0 (95% confidence interval 0.6 to 43.2). An increased mortality from cerebrovascular disease was still present for 19 years from first use. Deaths from cervical cancer increased fourfold and those from lung cancer doubled with 10 years' exposure.

The important significant findings coincide with national trends. Women's deaths from lung cancer increased by 67% from 1972 to 1992, although their incidence of smoking fell.[2] Overall, women's rates of cancer (excluding cancer in situ) increased by 34% compared with only 18% for men.[2] As exogenous hormones alter copper/zinc antioxidant mechanisms and amine metabolism and impair liver clearance of benzo[a]pyrenes, increases in vascular and mental illnesses and lung and liver cancers are predictable.[3] The rate of rise in breast cancer since 1962 has reflected hormone prescribing patterns.[4] This study records a relative risk of 1.5 (1.0 to 2.2) for breast cancer 5-9 years after last use of oral contraceptives. Where confidence intervals include 1.0, oral contraceptives are not proved to be risk free.

The collaborative reanalysis found a 25% increased risk of breast cancer among 154 000 women after the remarkably short exposure of 3 years; only 6% of women with breast cancer were longer users, compared with 13.5% of other women.[5] Therefore high susceptibility to malignancy may be associated with effects after shorter use and variable latency. If the women most likely to develop breast and ovarian cancers stop because of early side effects their apparent risk over 25 years would be reduced.

At enrolment healthy women were selected; relatively few were new takers. Losses to follow up (7200 ever and 4300 never users) mostly occurred before flagging of deaths began in 1977. Such biases helped to reduce the differences in death rate between users and never users. Late complications are not ruled out, especially among longer users. Claims that oral contraceptives protect women from ovarian cancer are invalid if exposures to fertility drugs and other hormone treatments are not recorded in women with a median age of 48.

There are enormous vested interests in studies of this kind. The medical profession needs to examine closely the facts behind the claims of overall safety.

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DoH seems to have underestimated incidence of venous thromboembolism in users of combined oral contraceptives

EDITOR—Mayor reports the Department of Health's change of view on the use of third generation oral contraceptives.[1] The department now proposes that women may be prescribed these newer oral contraceptives provided that they are "fully informed." It is reported that the new package insert will include a statement that the risk of deep venous thrombosis is 15 per 100 000 among women using second generation pills and 25 per 100 000 among users of third generation products. The source of the data that formed the basis of the Department of Health's estimates has not been revealed. Using an evidence based approach to this issue, we conducted a search on Medline and Embase using several terms: contraceptives, oral (oral contraceptive agents); thromboembolism; thrombophlebitis; venous thrombosis (vein thrombosis/deep vein thrombosis); pulmonary embolism (lung embolism); and incidence or cohort studies (cohort analysis). The search was restricted to studies published from 1985 onwards in order to focus on studies involving the newer low dose oral contraceptives. We found six relevant papers.

Incidence of venous thromboembolism (number of cases per 100 000) among all users of combined oral contraceptives in six studies

Study	Incidence	No of cases: No of woman years
Farmer et al 1997[2]	41	83:202 517
Pini et al, 1996[3]	62	37:59 603
Jick et al, 1995[4]	23.2	75:323 888
Gerstman et al, 1990[5]	5	94:177 607
Vessey et al, 1986[6]	39	3:7606
Porter et al, 1985[7]	8	3:37 807

From each of these we abstracted the crude population incidences of venous thromboembolic events (deep venous thrombosis and pulmonary embolism) (table). Rates vary between 8 and 62 per 100 000 exposed woman years and result in a pooled estimate of 36.5 per 100 000. The only studies with rates of less than 25 per 100 000—the rate that the Department of Health states is associated with the newer third generation combined oral contraceptives—are those of Jick et al (1995)[4] and Porter et al (1985),[7] Porter et al's estimate being based on three exposed cases.

We recently completed a further study on the general practice research database, in which we identified 320 cases of venous thromboembolism in users of combined oral contraceptives between 1992 and 1997. We found an incidence in women using combined oral contraceptives containing less than 50 µg oestrogen of 38 per 100 000. We believe that this is likely to be closer to the true incidence of venous thromboembolism in users of low oestrogen combined oral contraceptives. It is interesting that the Department of Health quotes a rate based on only one study when a body of evidence is available.

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