Letters

Website: **www.bmj.com**
Email: **letters@bmj.com**

The Swiss heroin trials

Trial is needed comparing decriminalisation of heroin with existing policy of prohibition

EDITOR—Farrell and Hall seem to have misunderstood the importance of the Swiss trials of heroin on prescription for addicts.[1] The call for a clinical trial of heroin versus methadone is irrelevant as these drugs cater for different segments of the addict population; no one suggests stopping methadone clinics. It is self evident that prescribing heroin will attract addicts who need the "buzz" and will not switch to methadone. These include dealers and pushers and those who succeed in obtaining funds through crime. Methadone clinics attract newer rather than hard core addicts. A logical policy for decriminalising heroin under medical supervision would have four steps: giving prescriptions of heroin to all addicts in or out of prison (which would gradually put criminals out of business); providing methadone clinics for those who will switch; weaning the addicts off the drugs; and providing a follow up programme to minimise relapse. The trial that is needed would compare a city region or country adopting this approach with a similar community continuing the existing policy of prohibition. This policy has already failed for the same reason that prohibition failed in the United States: it created an opportunity for the criminal mafias who dominate the drug scene. The end points of a comparative trial should not be narrowly defined as conceived by Farrell and Hall; they should include the numbers of new addicts, mortality and morbidity among addicts and former addicts, the impact on spread of HIV infection and hepatitis B both inside and outside prisons, and statistics for drug related crime (allegedly reduced by 60% in the Swiss trials). The economic gain to the community from heroin clinics will include the street price forgone by the clinics' clients, which would otherwise be stolen from members of the community. This is a massive gain over and above the similar gain from methadone clinics. The time has come for the medical management of heroin addicts to be submitted to the disciplines of clinical pharmacology and epidemiology, including, ideally, randomised controlled trials.

Apart from the impact on problems caused by hard drugs, the new approach will be essential for resolving issues surrounding soft drugs. Marijuana is safer than alcohol or tobacco, but legalisation is inhibited by the fear that pushers of hard drugs can recruit users of soft drugs.

G R Venning *Consultant in pharmaceutical medicine*
Pharmaceutical Research Services, High Wycombe, Buckinghamshire HP13 6QG

1 Farrell M, Hall W. The Swiss heroin trials: testing alternative approaches. *BMJ* 1998;316:639. (28 February.)

Further studies of heroin treatment are needed

EDITOR—On the basis of a trial in Switzerland,[1] Farrell and Hall conclude that medically prescribed heroin is likely to have only a limited role in the future.[2] It is hard to know how any judgment can be made about this approach after only one randomised control trial,[3] one case-control study,[4] and the large but uncontrolled study that the authors commented on.[1]

Farrell and Hall are right to emphasise the difficulty of disentangling the contribution of comprehensive social and psychological inventions in the impressive results obtained in this population.[1] After more than three decades of research evaluating the effectiveness of methadone maintenance treatment it is safe to conclude that such interventions improve outcomes but difficult to be much more precise than this. Social and psychological interventions probably improve results of virtually all interactions between patients and the healthcare system.

The authors say that the proposal to conduct a heroin trial in Australia damaged support for harm reduction. This is arguable. The mood in Australia has generally been more conservative over the past two years. The controversy over the heroin trial in Australia probably contributed to major improvements in a local methadone programme and certainly led directly to a commitment and funding for research on an expanded range of pharmacological treatments for heroin dependence.

The authors question whether Australia is in the middle of a national heroin crisis. If a sixfold increase in mortality from drug overdose during the past 16 years[5] is not a crisis it is hard to know what would be.

The Swiss heroin trial may have been more expensive than routine prescription methadone. But trials of new treatment are invariably more costly than providing well established treatments as a routine. Heroin and methadone are both cheap to produce. The cost of methadone represents under 5% of the costs of methadone maintenance treatment. There is no good reason to believe that heroin treatment will be considerably more expensive than methadone treatment.

Most important, Farrell and Hall endorse studies that will determine the comparative usefulness and cost effectiveness of injectable heroin and methadone maintenance treatment. The 71% support for heroin maintenance shown in a referendum in Switzerland in September 1997 (with majorities in all 26 cantons) suggests that the Swiss were not confused about these issues.

Rigorously conducted trials of medically prescribed heroin must be conducted soon lest we repeat the history of methadone maintenance treatment: the failure to conduct such studies when they were still possible proved costly.

Alex Wodak *Director*
Alcohol and Drug Service, St Vincent's Hospital, Sydney, NSW 2010, Australia

1 Uchtenhagen A, Gutzwiller F, Dobler-Mikola A, eds. *Programme for a medical prescription of narcotics: final report of the research representatives. Summary of the synthesis report.* Zurich: University of Zurich, 1997.
2 Farrell M, Hall W. The Swiss heroin trials: testing alternative approaches. *BMJ* 1998;316:639. (28 February.)
3 Hartnoll R, Mitcheson M, Battersby A, Brown G, Ellis M, Fleming P, et al. Evaluation of heroin maintenance in controlled trial. *Arch Gen Psychiatry* 1980;37:877-84.
4 McCusker C, Davies M. Prescribing drug of choice to illicit heroin users: the experience of a UK community drug team. *J Subst Abuse Treatment* 1996;13:521-31.
5 Hall W, Darke S. *Trends in opiate overdose deaths in Australia 1979-1995.* Sydney: University of New South Wales, 1997. (NDARC technical report.)

Authors' reply

EDITOR—We used the Swiss trial of prescribing heroin to counter the unrealistic expectations of its impact exemplified by Venning, who asserts that heroin prescribing will eliminate the black market, drug related crime, and the recruitment of new users of heroin.

Venning's letter is lacking in supporting evidence, relying on appeals to "self evident" facts and "lessons" from the history of alcohol prohibition that are uninformed by recent scholarship (for example, the article by Tyrell).[1] A confusion between heroin prescribing as a therapeutic option of last resort and the repeal of prohibition of heroin[2] was one of the reasons why Australia did not proceed with a trial of heroin prescribing.

Wodak contests our assertion that the Swiss model of on-site heroin prescribing is likely to be an expensive, minority treatment option. It is costly to ensure that heroin is not diverted between manufacture and

administration, and for staff clinics to provide extended hours to supervise self treatment with heroin. The costs are calculated to be between five and 10 times those of oral methadone treatment. The high level of supervision that was necessary to address public anxieties about heroin prescribing and the risks of diversion was an interesting aspect of the trial.

The increased rate of deaths in people taking heroin in Australia certainly presents a major public health problem, but we doubt that "crisis" is the best way to describe it. The increase has occurred over two decades, and most deaths are now among people who started using heroin a decade or more ago. "Heroin crises," like "drug wars," tend to prompt ill considered and disproportionate policy responses.

The relation between the debate over a trial of heroin and the trial of alternative pharmacotherapies in Australia is more complex than Wodak suggests. A large trial of buprenorphine predated the debate over trials of heroin, as did plans for trials of other agents. The failure to proceed with the heroin trial did produce a commitment to partially fund these other trials, which would not have happened if the trial had proceeded. But the only trials that have been funded to date (with A$1.4m (£518 500)) have been three small trials of naltrexone maintenance (after accelerated withdrawal under general anaesthesia), a treatment of uncertain efficacy whose prominence in Australia has owed much to the debate about a heroin trial.

Wayne Hall *Executive director*
National Drug and Alcohol Research Centre, Sydney, Australia

Michael Farrell *Senior lecturer*
National Addiction Centre, Institute of Psychiatry, London SE5 8AF

1 Tyrell I. The US prohibition experiment: myth, history and implications. *Addiction* 1997;92:1405-9.
2 Farrell M, Strang J. Confusion between the drug legalisation and drug prescribing debate. *Aust Drug Alcohol Rev* 1990;9:364-8.

Recovered memories of childhood abuse

We must tell patients that they were not to blame

Editor—Pope welcomes the recent report from the Royal College of Psychiatrists, which counsels caution when treating patients with "recovered memories" of sexual abuse in childhood.[1] This report may encourage disbelief of patients presenting with any memory of childhood abuse.

Child sexual abuse is common in the United Kingdom.[2] It is associated with long term physical and psychological sequelae.[3] Its victims are reluctant to disclose their histories to doctors: only one in 20 will try to do so.[4] They wait an average of 17 years after the abuse has occurred, and expect to be disbelieved and blamed.[5]

Since 1896, when Freud radically altered his opinions and pronounced that his patients' stories of incestuous abuse were the stuff of fantasy, society has found it difficult to confront the reality of child abuse. There is a national organisation that represents people who allege that they have been falsely accused of perpetrating abuse, but there is no one body to which adult survivors can turn for help and advice. Should any of our patients be desperate enough to entrust us with their stories of childhood sexual abuse then the least we can do is to believe them and tell them that they were not to blame.

J K Ilsley *General practitioner*
Nunwell Surgery, Bromyard, Herefordshire HR7 4BZ

1 Pope HG Jr. Recovered memories of childhood sexual abuse. *BMJ* 1998;316:488-9. (14 February.)
2 Baker A, Duncan SP. Child sexual abuse: a study of prevalence in Great Britain. *Child Abuse & Neglect* 1985;9: 457-67.
3 Arnold PR, Rogers D, Cook DAG. Medical problems of adults who were sexually abused in childhood. *BMJ* 1990;300:705-8
4 Lechner ME, Vogel ME, Garcia-Shelton LM, Leichter JL, Steibel KR. Self-reported medical problems of adult female survivors of childhood sexual abuse. *J Fam Pract* 1993;36:633-8.
5 Kendall-Tackett MA, Simon AF. Perpetrators and their acts: data from 365 adults molested as children. *Child Abuse & Neglect* 1987;11:237-45.

People with memories of abuse must be given reassurance

Editor—I agree with the recommendations by the Royal College of Psychiatrists reported in Pope's editorial.[1] One problem with memories of sexual abuse in childhood is the absence of empirical evidence. In certain cases the "recovered" memories have been shown to be based on hysteria, fantasy, malicious invention, or lies. These cases, however, are surely the exception that proves the rule.

There is an epidemic of child sexual abuse in the world today. In the United States, several million cases of child abuse and neglect are "indicated" each year, and this figure continues to climb. These cases are backed up by the authority of the government entities entrusted by us all to investigate child abuse.

Such a widespread phenomenon could not have simply sprung into existence in the past 10 or 20 years, alongside the survey instruments that now prove its existence. Childhood sexual abuse is far older—perhaps as old as the hills themselves. What is new is society's willingness to look at the problem; the masses of adults waking up to the terrible reality that violence was perpetrated against them at the most vulnerable time in their lives; the millions of adults throughout the world speaking out on their own behalf and for the children of today who are being abused in equal or greater numbers, yet continue to be silenced or ignored. There may be disputes over methodology during the initial phase of studying the problem, but that must not distract us from marshalling all necessary resources for the prevention, treatment, and punishment of all cases of abuse.

Traumatic memory occurs on many different levels. The verbal component is what we are certain of in a rational sense—I did this, said that, saw them, etc. Trauma is hard to explain. however, because it overwhelms the senses. Survivors of a traumatic experience may fragment their memories into various components—the touch, the smell, the sight, and the sound. Once a memory is fragmented, it must be even harder to put it in words.

Many of us who have survived profoundly traumatic experiences spend the rest of our lives piecing all those fragments together—only to be attacked by misguided psychiatrists and researchers as people with "false memories." It is a dark day for the psychiatric profession when a consensus seems to have been constructed against the telling of stories by survivors of violence. If we are ever to turn back the tide against the abuse of children we must begin by listening to these stories—and giving the story tellers the benefit of the doubt.

Carl-David Birman *Director*
Safety, New York, NY 11218-4315, USA

1 Pope HG Jr. Recovered memories of childhood sexual abuse. *BMJ* 1998;316:488-9. (14 February.)

Author did not declare his affiliation

Editor—Pope's editorial on recovered memories of sexual abuse in childhood[1] did not inform readers of his bias in the area of dissociative amnesia. He is a board member of the False Memory Syndrome Foundation, an organisation that advocates for people accused of sexually abusing children.

I have experienced dissociative amnesia and recovered memories of sexual abuse in childhood, and I found enough corroboration to meet the necessary legal standard of evidence to prove my charges in a landmark civil suit. My father (who at trial admitted to fondling another child) and his second wife have reported paying membership dues to the False Memory Syndrome Foundation.

Details of other cases of recovered memories of childhood abuse which have found strong corroboration can be found on the following website:

http://www.brown.edu/Departments/Taubman_Center/Recovmem/Archive.html

Jennifer Hoult *Professional musician*
New York, NY 10025, USA

1 Pope HG Jr. Recovered memories of childhood sexual abuse. *BMJ* 1998;316:488-9. (14 February.)

Some memories may be false, but some may be true

Editor—Pope's editorial on the Royal College of Psychiatrists' recommendation on how to treat people with recovered memories of childhood sexual abuse[1] conformed to the views of the false memory societies and some of their scientific advisers, but it was at variance with the current scientific consensus among memory experts.[2]

The apparent forgetting and recovery of memories of trauma is not a recent observation confined to patients having treatment for actual or suspected abuse in childhood.

The forgetting of traumatic incidents during this century's two world wars has been repeatedly described by some of Britain's most eminent psychologists and psychiatrists. Consistent with this, recent research indicates that the forgetting and subsequent recovery of memories is associated with a wide range of traumatic incidents, including the witnessing or experiencing of injury, violence, and death. Memory recovery often seems to occur spontaneously, before the involvement with therapists. Corroborative evidence of the essential accuracy of the recovered memories, sometimes of high quality, has been found in substantial numbers of cases.[3] Pope offers no explanation for these data.

Moreover, these repeated observations are supported by biological studies of trauma and memory. Whereas heightened states of arousal often improve memory consolidation, extraordinarily high concentrations of catecholamines or other neuropeptides at the time of the trauma, perhaps in combination with a failure to release sufficient cortisol, may produce amnesia.[4] Several studies have shown reduced hippocampal volume in traumatised subjects, a potentially reversible anatomical change that may have important implications for memory functioning. Cognitive psychology, too, recognises that ordinary memory relies for its efficiency as much on the ability to inhibit unwanted material as on the ability to gain rapid access to relevant material. Experimental studies show the inhibition of memory retrieval and the existence of a subgroup of people with poor memories for negative experiences.[3]

The implication that recovered memories are invariably the product of "recovered memory therapy" is circular and lacks empirical support.[5] Likewise, Pope's discussion of existing methods and findings relies on its own set of questionable assumptions. Rather than simply attack the idea that traumas may be forgotten, we need to develop theories that can account for all the available data. At present it looks as though one such theory will have to admit the essential accuracy of some recovered memories while acknowledging that others may be false.

Chris R Brewin *Professor of psychology*
Department of Psychology, Royal Holloway, University of London, Egham, Surrey TW20 0EX

1 Pope, HG Jr. Recovered memories of childhood sexual abuse. *BMJ* 1998;316:488-9. (14 February.)
2 Brewin CR. The scientific status of recovered memories. *Br J Psychiatry* 1996;169:131-4.
3 Brewin CR, Andrews B. Recovered memories of trauma: phenomenology and cognitive mechanisms. *Clin Psychol Rev* (in press).
4 Yehuda R, Harvey P. Relevance of neuroendocrine alterations in PTSD to memory-related impairments of trauma survivors. In: Read JD, Lindsay DS, eds. *Recollections of trauma: scientific evidence and clinical practice*. New York: Plenum Press, 1997:221-42.
5 Pope KS. Memory, abuse and science: Questioning claims about the false memory syndrome epidemic. *Am Psychol* 1996;51:957-74.

There is no evidence that therapists implant memories

Editor—Pope states in his editorial that he has found no evidence of repression in classical or scientific literature.[1] The same argument holds true for the opposite stance. There is no evidence that therapists have implanted false memories of childhood trauma in classical (or modern) literature—nor is there clear evidence of this in scientific literature.

The popular belief that therapists can implant memories "does not spare investigators the burden of providing a rigorous, methodologically convincing demonstration of its existence," (to use Pope's words).

Lynn Crook *Editor, Treating Abuse Today*
Richland, WA 99352, USA

1 Pope HG Jr. Recovered memories of childhood sexual abuse. *BMJ* 1998;316:488-9. (14 February.)

Author's reply

Editor—I strongly agree with Ilsley and Birman that sexual abuse in childhood is both common and deplorable. It does not logically follow, however, that such abuse can create "repressed memories." Nor is my scepticism about the validity of repressed memories an attempt to refute the extent of sexual abuse itself. I am not a board member of the False Memory Syndrome Foundation, but rather a member of the foundation's scientific advisory board, which I volunteered to join after witnessing the tragedies perpetrated by "recovered memory therapy." This position creates no conflict of interest, since I receive no payment of any sort from it, nor does the foundation have any influence over what I do or write. The scientific validity of repressed memory is not improved simply because the concept is venerable and endorsed by personal testimonials; because it seems plausible that survivors would fragment their memories; or because there exists a brain mechanism which might explain it if, hypothetically, it did occur. I have discussed elsewhere the fallacies inherent to these arguments.[1] The existence of repressed memory will be established only by sound prospective studies meeting basic minimum methodological standards.[2]

Here I diverge from Brewin, who argues that such evidence already exists and that the "consensus among memory experts" goes against me.[2 3] I would like to point out the following:

1) in an unselected review of 63 studies, comprising more than 10 000 victims of all manner of traumas, none reported repressed memories[2];

2) in a review of 45 other studies of the sequelae of childhood sexual abuse, examining 3369 victims, amnesia is nowhere described[4];

3) in a survey of 301 board certified American psychiatrists that I carried out only 23% answered that there was "strong evidence" for the validity of "dissociative amnesia," with 19% answering "little or no evidence" (unpublished data);

4) American courts in the last several years have overwhelmingly ruled "repressed" and "recovered" memory scientifically inadmissible[5]; and

5) numerous scholarly reviews have questioned the validity of these concepts.

In the light of these observations, it seems doubtful that I, or the Royal College of Psychiatrists, or the false memory societies, voice an idiosyncratic or minority opinion.

Harrison G Pope Jr *Associate professor of psychiatry*
Harvard Medical School, Boston, MA 02115, USA

1 Pope HG Jr. *Psychology astray: fallacies in studies of "repressed memory" and childhood trauma*. Boca Raton, FL: SIRS, 1997.
2 Pope HG Jr, Hudson JI, Bodkin JA, Oliva P. Questionable validity of 'dissociative amnesia' in trauma victims. Evidence from prospective studies. *Br J Psychiatry* 1998;172:210-5.
3 Brewin CR. The scientific status of recovered memories. *Br J Psychiatry* 1998;172:216-7.
4 Kendall-Tackett KA, Williams LM, Finkelhor D. Impact of sexual abuse on children: a review and synthesis of recent empirical studies. *Psychol Bull* 1993;113:164-80.
5 Johnston M. *Spectral evidence: the Ramona case: incest, memory and truth on trial in Napa Valley*. Boston: Houghton Mifflin, 1997.

Mouth care and skin care in palliative medicine

Editor—We advocated a pragmatic approach to mouth and skin care in the ABC of Palliative Care.[1] Not all the suggestions in the subsequent correspondence followed the same principle.[2]

Lucas and Roberts rightly point to the evidence for chlorhexidine in reducing oral bacteria. They fail to point out that chlorhexidine alters taste and can damage oral mucosa and that some randomised trials have shown it to be no better than water in preventing mucositis caused by treatments such as chemotherapy.[3] Together with the oral discomfort that occurs on application, chlorhexidine is not the panacea in palliative care that they would have us believe.

Pemberton and Thornhill reiterate the continuing uncertainty over the origin of apthous ulceration,[2] but they contradict themselves in complaining about treating apthous ulcers as infective and then admitting the importance of secondary infection and the appropriateness of using antimicrobial agents.

Davies, along with several of the correspondents, disagrees with our management of a dry mouth.[2] Hyposalivation is a problem in patients, and two correspondents recommend salivary stimulants. Chewing gum, suggested by two correspondents, has not proved helpful in our patients with a persistently dry mouth. Davies et al have shown that pilocarpine stimulates salivation but at the cost of significantly more adverse effects.[4] When patients were given a choice, they thought pilocarpine was no better than a substitute for saliva based on mucin.[4] In a previous study patients found porcine mucin to be no better than water.[5] Patients seem to find sprays containing water or cool, pleasant drinks most helpful.

Dixon and Hockley chastise us for failing to be sufficiently multidisciplinary by not suggesting surgical debridement in managing pressure sores and malignant ulcers.[2] We agree that this approach has a role in some patients, but for nearly all patients with very advanced disease it is

inappropriate because they are too ill or they are adamant that they wish no further intervention at the end of their lives.

Treatments must be chosen with patients. In reality, however, patients who are asked for their preferences do not always choose what professionals believe to be the correct treatment. In addition, when evidence is contradictory, it can be difficult to accept that the simplest approaches may be the most appropriate. Perhaps it was the simplicity of our approach that caused these correspondents difficulty.

Claud Regnard *Consultant in palliative medicine*
Sarah Allport *Clinical nurse manager*
Lydia Stephenson *Senior physiotherapist*
St Oswald's Hospice, Newcastle upon Tyne
NE3 1EE

1 Regnard C, Allport S, Stephenson L. ABC of palliative care: Mouth care, skin care, and lymphoedema. *BMJ* 1997;315:1002-5.
2 Lucas VS, Roberts GJ, Dixon JM, Hockley J, Pemberton M, Thornhill MH, Davies A. Mouth care and skin care in palliative medicine [correspondence]. *BMJ* 1998;316:1246-7. (18 April.)
3 Dodd MJ, Larson PJ, Dibble SL, Miaskowski C, Greenspan D, MacPhail L, et al. Randomized clinical trial of chlorhexidine versus placebo for prevention of oral mucositis in patients receiving chemotherapy. *Oncology Nursing Forum* 1996;23:921-7.
4 Davies AN, Daniels C, Pugh R, Sharma K. A comparison of artificial saliva and pilocarpine in the management of xerostomia in patients with advanced cancer. *Palliat Med* 1998;12:105-11.
5 Sweeny MP, Bagg J, Baxter WP, Aitchison TC. Clinical trial of a mucin-containing oral spray for treatment of xerostomia in hospice patients. *Palliat Med* 1997;11:225-32.

Number needed to harm should be measured for treatments

EDITOR—The concept of number needed to treat was an attempt to introduce both simplicity and objectivity into the evaluation of treatment. It is helpful both on a large scale when treatments are compared and care is commissioned and on the personal level when doctor and patient choose the management for the individual. The number needed to treat gives a comparison of treatments and outcomes that both doctors and patients should understand.

One problem of this unimodal numerical scale for measuring the likely outcome of a treatment is that it oversimplifies the issues and may overvalue the treatment by ignoring its risks. Treatments may harm patients in various ways, the importance of which will depend on the disorder being treated as well as the nature of the harm. In a minor illness a potentially fatal treatment would not be acceptable even if the risk were fairly small. If a condition is uniformly fatal if untreated the risk of death or disability from the treatment is likely to be acceptable and a period of pain or discomfort may be a small price to pay. Not only are all adverse effects not equal but their importance depends as much on their context as their nature.

Another problem with adverse effects is that we can seldom be as accurate in guessing risk as we are in measuring benefit. The therapeutic effect of a drug is usually unimodal and obvious. Controlled trials should separate the therapeutic effect from the placebo effect and allow an objective measurement of the real therapeutic benefit. One drug can, however, have many potential adverse effects, only some of which can be anticipated from its pharmacology or have been recognised when it is licensed. The incidence of common problems can be found from the results of clinical trials, but the recognition of more subtle effects often takes years. Even death and disability may not be recognised as therapeutic misadventure if the prevalence is small or the onset delayed. The risk will always be underestimated.

We must not ignore the risk of treatment even if it is hard to measure. It may not be possible to devise a unimodal number needed to harm measurement, but a compensating negative measure is essential if we are not to delude ourselves and our patients about the value of treatment.

A possible solution might be to separate adverse effects into several grades, on the basis of severity, reversibility, and usual duration. These might be: number needed to kill, number needed to disable, number needed to make you ill, and number needed to annoy. The concept of attaching a price list to the therapeutic menu should not stop with the cost of the pills.

Arnold Zermansky *General practitioner*
Dib Lane Practice, Leeds LS8 3AY

Systematic review of trials comparing antibiotic with placebo for acute cough in adults

Data do not justify study's conclusions

EDITOR—Chapman has highlighted the confusion caused by the different interpretations of the report by the International Agency for Research on Cancer on the effects of passive smoking.[1] By ignoring the size and direction of the effect and focusing on the lower limit of the confidence interval the agency came to the erroneous conclusion that passive smoking does not cause lung cancer. Unfortunately, Fahey et al have fallen into the same trap in reporting the results of a systematic review of the use of antibiotics in acute cough.[2]

They state categorically in their discussion: "This systematic review shows that antibiotic treatment has no effect on the resolution of acute cough." This conclusion is not justified by the data in their review. Two of the outcomes measured—the resolution of productive cough and clinical improvement—show a pooled effect that favours antibiotics but does not reach significance at the 95% level when a random effects model is used. The authors seem to have confused the significance of these findings with the size of the effect. There is around a 1 in 40 chance of this pooled result arising because of random variation rather than because of a real difference between antibiotic and placebo; this is hardly grounds to claim that the review shows that antibiotics have no effect.

The authors do not show an even handed approach when they deal with the data concerning the efficacy of antibiotic and side effects of treatment. In the case of efficacy they state that "antibiotic treatment was no better than placebo," and in the case of side effects they state that the data showed "a non-significant increase in the risk of side effects from antibiotics." They then proceed to exclude the only trial that showed more side effects in the placebo group than the antibiotic group (on the grounds that this exclusion reduces heterogeneity) and find that the pooled result is then significant.

Excluding a study because of the direction of its result is not an acceptable method of generating significance. Heterogeneity in this outcome was not excessive ($\chi^2 = 7.80$, df = 5, $P > 0.01$), and the same technique could have been used to generate a significant benefit for the outcome of resolution of cough by excluding Williamson's trial. Might the review process have been influenced by the conclusions?

C J Cates *Editor, Cochrane Airways Review Group*
Manor View Practice, Bushey Health Centre,
Bushey, Hertfordshire WD2 2NN

1 Chapman S. The hot air on passive smoking. *BMJ* 1998;316:945. (21 March.)
2 Fahey T, Stocks N, Thomas T. Quantitative systematic review of randomised controlled trials comparing antibiotic with placebo for acute cough in adults. *BMJ* 1998;316:906-10. (21 March.)

Too few subjects were studied for useful conclusions to be drawn

EDITOR—Objective assessment of the results of systematic reviews is essential, as clinicians may place greater emphasis on the conclusions reached in such reviews than they would on those of any of the individual trials. Fahey et al state that their quantitative systematic review shows that "antibiotic treatment has no effect on the resolution of acute cough" and that "treatment with antibiotic may incur side effects in a few patients."[1] We do not believe that this conclusion can be reached on the basis of the results of the review.

The study reported results with regard to three main outcome measures. The relative risks obtained for the effect of antibiotic treatment compared with placebo on the resolution of cough was 0.85 (95% confidence interval 0.73 to 1.00), for the effect on clinical improvement at re-examination it was 0.62 (0.36 to 1.09), and for the effect on side effects it was 1.51 (0.86 to 2.64). Despite the differences found in the review, none of the results reaches significance as all the 95% confidence intervals include 1.00. It is important to note how wide the confidence intervals are for each result. This reflects the small numbers of patients available for comparison for each outcome measure.

Of particular interest is the finding that, despite its large width, the 95% confidence interval favours antibiotics for an effect on

both resolution of cough and clinical improvement at re-examination; this suggests a trend favouring the use of antibiotics over placebo.[2] For resolution of cough there is a 95% chance that with more patients a benefit of antibiotics would be found for resolution of acute cough somewhere between a relative risk of 0.73 and one of 1.00. There may also be a benefit in terms of clinical improvement at re-examination of up to 0.36, or a detriment of up to 1.09 (the 95% confidence interval). For side effects the 95% confidence interval favours placebo, but a study with larger numbers might find that antibiotics have fewer side effects than placebo, with a relative risk of up to 0.86.

An objective analysis of these results suggests that the number of subjects studied was too small for any useful conclusions to be drawn; a potentially important benefit favouring the use of antibiotics in acute cough cannot, however, be excluded. Whether any benefit found would be clinically relevant (after the magnitude of benefit, cost, and side effects has been taken into account) is also yet to be answered. Further trials are warranted.

Thomas P Shakespeare *Specialist registrar in radiation oncology*
Liverpool Hospital, Liverpool, NSW 2170, Australia

Rachael C Bourke *Medical student*
University of Adelaide Medical School, Adelaide, South Australia, 5001, Australia

1 Fahey T, Stocks N, Thomas T. Quantitative systematic review of randomised controlled trials comparing antibiotic with placebo for acute cough in adults. *BMJ* 1998;316:906-10. (21 March.)
2 Braitman LE. Confidence intervals assess both clinical significance and statistical significance. *Ann Intern Med* 1991;114:515-7.

Quality scores showed poor agreement

Editor—Fahey et al report their meta-analysis of the literature on the use of antibiotics for acute cough in adults[1] but would have done better to stick to a good literature review, albeit that this has been done before.[2] They left their inclusion criteria broad, presumably to increase the numbers of papers to review. I remain to be convinced, however, that it is sensible to combine trials that may have included 12 year olds with a one day history of cough and no findings on examination with trials in 90 year olds with a three week history as well as fever, malaise, purulent sputum, and findings on auscultation. They excluded patients with chronic obstructive pulmonary disease but did not consider those with asthma.

In order to combine six small trials (of 45-207 patients, total 700) they chose outcome measures that necessitated the exclusion of a trial in 829 patients. This makes no sense. Small trials are more likely to be of poor quality,[3] and so it is important that this is properly assessed. Their kappa scores, however, show poor agreement on scoring quality, particularly on the most important category, selection bias. Scrutiny of the data given on the website makes me doubt their assessment even more. For example, a trial of 45 patients with only a 20% recruitment rate and a 29% rate of loss to follow up scores 9 out of 12 for quality.

The authors relaxed their original criteria in order to include a trial in patients as young as 8, which they give a quality score of only 7. This study of 72 patients goes on to contribute a weight of 41.3% in one of the outcome meta-analyses, and no mention is made of the potential for bias.

The authors overstate their conclusions by saying that resolution of cough was not affected by antibiotic treatment but that side effects were more common in the antibiotic group. In fact, neither result reaches significance.

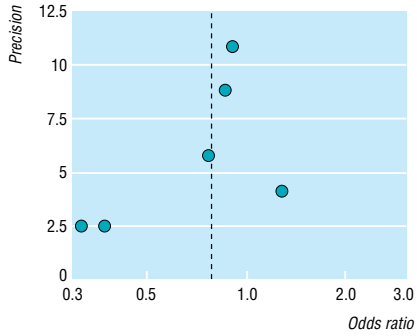
The use of systematic reviews and meta-analysis has brought a valuable new dimension to clinical research[3 4] and encouraged the introduction of evidence based medicine.[5] It is still in its youth, and such published research must be of high quality so that all doctors become convinced of its potential.

Jessica Harris *General practitioner*
Bacon Road Medical Practice, Norwich NR2 3QX

1 Fahey T, Stocks N, Thomas T. Quantitative systematic review of randomised controlled trials comparing antibiotic with placebo for acute cough in adults. *BMJ* 1998;316:906-10. (21 March.)
2 MacKay DN. Treatment of acute bronchitis in adults without underlying lung disease. *J Gen Intern Med* 1996;11:557-62.
3 Mulrow CD, Oxman AD. Cochrane collaboration handbook. In: *Cochrane Library* [database on disk and CD ROM]. Issue 2. Oxford: Update Software, 1996.
4 Chalmers I, Altman D, eds. *Systematic reviews*. London: BMJ Publishing, 1995.
5 Sackett D, Richardson WS, Rosenburg W, Haynes RB. *Evidence-based medicine*. London: Churchill Livingstone, 1997.

Authors' reply

Editor—Cates bases his criticism on manipulation of the pooled effect estimates and our attributing the non-significant trend towards antibiotic as evidence of efficacy. Because of the substantial likelihood of bias we were deliberately cautious in attributing benefit to antibiotic.[1] The danger in systematic reviews, particularly those based exclusively on small trials, is not of statistical precision but of systematic bias and the production of false positive results.[2 3] Unfortunately, there is no statistical solution to this problem.[1] Funnel plot asymmetry from our systematic review (figure) shows that estimates of efficacy were far greater in the two smaller trials that contributed to the meta-analyses.[4 5] Thus we believe that we are correct in our cautious interpretation of the pooled results.



Funnel plot of six trials that contributed to outcome of productive cough at follow up. Pooled odds ratio (fixed effects model) is 0.78 (95% confidence interval 0.56 to 1.08)

In suggesting that there is a trend favouring the use of antibiotics over placebo, Shakespeare and Bourke fail to account for all the evidence that we presented. They are right that the number of subjects (700) in which the outcome of productive cough was based is small. They ignore, however, the 829 patients in the trial by Howie and Clark, which reported no difference between antibiotic and placebo but which we did not include in the pooled estimate because analysis was by episode of illness. Furthermore, as we reported, the trials with more positive results were smaller trials with substantial losses to follow up.[4 5]

We would have liked to include Howie and Clark's trial in the pooled analysis; we reported its results in detail because we wanted to emphasise its importance in the context of the evidence presented in our review. We agree with Harris's anxieties about the quality of individual studies, and this accounts for our cautious conclusions concerning pooled estimates. We presented losses to follow up because this allows readers to judge for themselves the quality of trials that contributed to the review. We agree with Harris that quality criteria and scoring systems may not distinguish high and low quality trials.

The results of our review should be seen in the context of the high prescribing of antibiotics for acute chest infection in otherwise healthy people throughout the developed world. We reported the number needed to treat (n = 11) and number needed to harm (n = 15) for clinical improvement—even if we accept the trend towards antibiotic as evidence of efficacy—to show that the clinical benefit of antibiotic is probably marginal. Further trials in higher risk groups are more likely to show important benefits for patients.

In collaboration with American colleagues we will update this review for the *Cochrane Library*. We will make explicit our concerns about potential biases in the updated version.

Tom Fahey *Senior lecturer in general practice*
Nigel Stocks *Clinical lecturer in general practice*
Division of Primary Care, University of Bristol, Bristol BS8 2PR

1 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.
2 Egger M, Davey Smith G. Misleading meta-analysis. *BMJ* 1995;310:752-4.
3 Egger M, Schneider M, Davey Smith G. Meta-analysis: Spurious precision? Meta-analysis of observational studies. *BMJ* 1998;316:140-4.
4 Dunlay J, Reinhardt R, Donn L. A placebo-controlled, double blind trial of erythromycin in adults with acute bronchitis. *J Fam Pract* 1987;25:137-41.
5 King D, Williams CW, Bishop L, Shechter A. Effectiveness of erythromycin in the treatment of acute bronchitis. *J Fam Pract* 1996;42:601-5.

Celebrity's death from cancer resulted in increased calls to CancerBACUP

EDITOR—It is known that a patient with cancer can be influenced in her choice of treatment by the choice made by a famous person with the same disease. When Nancy Reagan, the wife of the then American president, chose a mastectomy in 1987, there was a subsequent 25% decrease in the number of women choosing breast conserving surgery.[1,2] A celebrity's death can have a similar powerful effect. The death of Diana, Princess of Wales, resulted in unprecedented public and media response.[3,4] The death of Linda McCartney in April has also shown that patients may be substantially affected by such a tragedy.

CancerBACUP's telephone information service answered 40 715 calls (daily average 160) in April 1997 to March 1998, 11 675 of which were related to breast cancer. When all lines are busy, calls are directed to a call logging machine; on average 500 calls a day are logged. BT provides data on "ineffective" calls to the freephone—that is, those in which the caller obtains the engaged signal when all the nurses and answering machines are busy. About 5500 calls are ineffective.

In the week after Linda McCartney's death (announced on Sunday 19 April), calls and inquiries about breast cancer increased substantially. Additional resourced lines increased the daily average number of calls to 204 (44 more calls). Seventy two calls daily (28 more calls) were about breast cancer, representing a 64% increase in the number of answered calls about breast cancer. In the same week, despite the extra open lines, the daily average number of calls logged to the answering machines doubled to 1008, the highest daily number being 1262 (figure). Altogether 1090 (14%) of the weekly calls obtained the engaged signal. As far as we can ascertain there were no factors other than Linda McCartney's death that affected use. The next highest number of logged calls outside that week was 1106 (on 24 February), the day after the announcement that cancer had overtaken heart disease as the major cause of death. Other publicity, such as the American tamoxifen prevention trial (early April) and the role of anti-angiogenesis agents (early May), had a minor effect compared with that about Linda McCartney's death.

The death of a celebrity from a disease, so publicly explored, presumably forced women to face their own mortality. The result was a tremendous need for information, emotional support, and reassurance. Such a response indicates, perhaps, that however well a woman copes with a diagnosis of breast cancer, anxiety is never far from the surface.

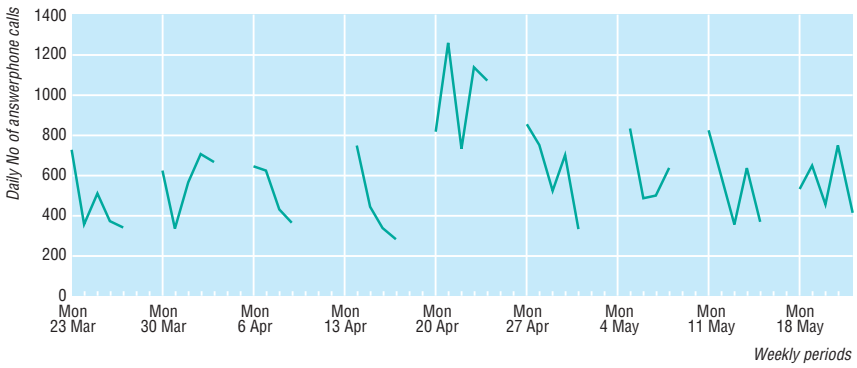
Markella Boudioni *Research officer*
Jean Mossman *Chief executive*
CancerBACUP, London EC2A 3DR
mboudioni@cancerbacup.org

Alison L Jones *Consultant oncologist*
Department of Clinical Oncology, Royal Free Hospital, London NW3 2QG

Geraldine Leydon *Research fellow*
Klim McPherson *Professor of Public Health Epidemiology*
Cancer and Public Health Unit, Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London WC1E 7HT

CancerBACUP exists to meet information needs of patients with cancer and their relatives and friends.

1 Wise J. Celebrities influence the public. *BMJ* 1998;316:801. (14 March.)
2 Nattinger AB, Hoffmann RG, Howell-Pelz A, Goodwin JS. Effect of Nancy Reagan's mastectomy on choice of surgery for breast cancer by US women. *JAMA* 1998;279:762-6.
3 Morgan-Jones R, Smith K, Oakley P. The "Diana effect." *BMJ* 1998;316:1750-1. (6 June.)
4 Shevlin M, Brundsen V, Walker S, Davies M, Ramkalawan T. Death of Diana, Princess of Wales. *BMJ* 1997;315:1467.



Daily number of calls received by answerphone (that is, not answered by nurses) on each working day Monday 23 March to Friday 22 May 1998. Vertical lines represent Mondays; two Mondays were public holidays

Sumatriptan is not the only analgesic used inappropriately

EDITOR—As Gaist et al report, the problem of overuse of sumatriptan is of considerable concern.[1] This is particularly so in the context of chronic daily headache.[2] Catarci et al have suggested that sumatriptan may replace ergotamine in overuse syndromes.[3] Staff at the headache clinic at the National Hospital in London have now seen patients who use sumatriptan, naratriptan, or zolmitriptan daily. Only overuse of sumatriptan has been observed in patients who have not previously used another acute antimigraine compound, but it seems reasonable to speculate that the problem may be seen with any triptan.

The core of this problem is that daily or near daily use of any triptan is, with few exceptions, inappropriate. Moreover, daily or near daily use of any acute antimigraine compound available in the United Kingdom may lead to appreciable management problems—in particular, headache associated with analgesic.[4] The commonest cause of this among patients seen in the headache clinic is overuse of compound analgesics, particularly those that include codeine phosphate. If daily or very frequent headache is as common in the United Kingdom as it is in the United States—in 4-5% of the population[5]—overuse of various painkillers is probably a considerable public health issue and has not received adequate attention. Our experience suggests that the issues raised by Gaist et al are just part of an epidemic.

Peter J Goadsby *Reader in clinical neurology*
Institute of Neurology, London WC1N 3BG

1 Gaist D, Tsiropoulos L Sindrup SH, Hallas J, Rasmussen BK, Kragstrup J, et al. Inappropriate use of sumatriptan population based register and interview study. *BMJ* 1998;316:1352-3. (2 May.)
2 Silberstein SD, Lipton RB, Sliwinski M. Classification of daily and near-daily headaches: a field study of revised IHS criteria. *Neurology* 1996;47:871-5.
3 Catarci T, Fiacco F, Argentino C, Sette G, Cerbo R. Ergotamine-induced headache can be sustained by sumatriptan daily intake. *Cephalalgia* 1994;14:374-5.
4 Mathew NT. Drug-induced headache. *Neurol Clin* 1990;8:903-12.
5 Scher A, Stewart WF, Liberman J, Lipton RB. Prevalence of frequent headache in a population sample. *Headache* 1997;37:330.

Suicide in patients with stroke

Depression may be caused by symptoms affecting lower urinary tract

EDITOR—In their paper on suicide in patients with stroke Stenager et al commented on the prevalence of depression after stroke.[1] If the underlying causes of this depression can be elucidated and treated then the risk of suicide may be lowered.

One such cause may be symptoms affecting the lower urinary tract (urinary incontinence, frequency, nocturia, and urgency), as self reported depression is related to such symptoms.[2] A total of 3592 questionnaires that were developed for a large Medical Research Council study on incontinence in Leicestershire have been analysed. The prevalence of self reported depression increased from 15% in patients with stroke without urinary symptoms to 32% in those who had had a stroke and urinary symptoms.

Symptoms affecting the lower urinary tract should not be discounted when assessing survivors of stroke in the community because they can be treated and hence could play an active part in reducing depression and therefore suicide.

K R Brittain *Research associate*
Division of Medicine for the Elderly, University of Leicester, Leicester LE1 7RH

C M Castleden *Professor*
Leicester General Hospital, Leicester LE5 4PW

1 Stenager EN, Madson C, Stenager E, Bolsden J. Suicide in patients with stroke: epidemiological study. *BMJ* 1998;316:1206. (18 April.)
2 Brittain KR. Urinary symptoms and depression in stroke survivors. *Age Ageing* 1998;27(suppl):72-3.

Future studies should consider the role of cerebrovascular disease

EDITOR—The epidemiological study by Stenager et al on the risk of suicide after stroke is the first study of its kind and highlights the prime importance of detecting mood disorder in patients with stroke.[1] However, the conclusion that society should take more interest in the psychosocial aspects of living with the impairment imposed by stroke underplays the role of organic brain damage imposed by cerebrovascular disease. As the prevalence of depression is higher in stroke than in disorders with a similar degree of disability,[2] closer scrutiny of the brain injury may be required. Indeed, one study of suicidal ideation after stroke found anterior brain lesions to be associated with suicidal thinking immediately after a stroke.[3] A possible explanation for the likely overrepresentation of suicidal thinking and completed suicide in patients with stroke is the high prevalence of lesions disrupting frontal and subcortical brain circuitry, either as lacunar infarcts or strategic cortical infarcts affecting the frontal lobe(s). Such lesions are associated with both depression[4] and impulsivity.[5]

Although the role of disability and social disadvantage after stroke cannot be understated, the contribution of damage to specific brain areas should continue to attract research. In this way, the study of cerebrovascular disease can complement epidemiological research into sociodemographic risk factors.

Rahul Rao *Senior lecturer in old age psychiatry*
Guy's Hospital, London SE1 9RT

1 Stenager EN, Madson C, Stenager E, Bolsden J. Suicide in patients with stroke: epidemiological study. *BMJ* 1998;316:1206. (18 April.)
2 Folstein MF, Maiberger R, McHugh PR. Mood disorder as a specific complication of stroke. *J Neurol Neurosurg Psychiatry* 1977;40:1018-20.
3 Kishi Y, Robinson RG, Kosier JT. Suicidal plans in patients with stroke: comparison between acute-onset and delayed-onset suicidal plans. *Int Psychoger* 1996;8:623-34.
4 Robinson RG, Morris PL, Fedoroff JP. Depression and cerebrovascular disease. *J Clin Psychiatry* 1990;51:26-31.
5 Kaye K, Grigsby J, Robbins LJ, Curzon B. Prediction of independent functioning and behaviour problems in geriatric patients. *J Am Geriatr Soc* 1990;38:1304-10.

Early diagnosis of cystic fibrosis can improve children's growth

EDITOR—Wald and Morris[1] seem to have examined carefully our article on the nutritional benefits of neonatal screening in cystic fibrosis[2] but they misunderstood some points and failed to grasp the potential advantages of preventing malnutrition in patients with cystic fibrosis.

They comment that our "study design is an ingenious one, but the analysis of the results is problematic." Ironically, the most ingenious feature is the very element they criticise with their comment that "a difficulty that is not discussed … is that the data in children under 4 years are subject to selection bias." Selection bias was one of the challenges we overcame in our study design. Our randomisation protocol was designed to include a group that had been screened at birth and a standard diagnosis (control) group.

Once the controls were identified by the unblinding process at 4 years of age, their anthropometric indices of nutritional status since birth were obtained by reviewing records; this information was incorporated into a "what if" analysis—a statistical analysis to determine how the control group would have compared with the screened group if all patients had been identified at birth. Although this was described in the original version of our paper it was deleted during editing but the paper still showed that significant differences persisted.

Wald and Morris ask for "a separate analysis restricted to follow up after the first four years." We completed the unblinding of controls last April and have accumulated sufficient data to show that significant differences persist. We have shown that if this analysis starts at 4 years of age the proportion of patients with cystic fibrosis who have heights above the 10th centile remains significantly greater in the screened group ($P = 0.042$).

Finally, the comment that "this trial provides no evidence of any benefit of screening" is inappropriate; not only are the nutritional advantages obvious from our study but also the psychological advantages of genetic counselling and the potential pulmonary benefits are evident.[3–5]

I strongly disagree with the concern implied by Wald and Morris that "early knowledge of a serious disorder will cause more harm than good if there is no effective remedy." Our assessment shows that malnutrition can be prevented by neonatal screening. Most doctors caring for patients with cystic fibrosis believe that interventions used to treat the respiratory disease are effective.

Philip M Farrell *Dean*
University of Wisconsin Medical School, Madison, WI 53706, USA
philip.farrell@mail.admin.wisc.edu

On behalf of the Wisconsin Cystic Fibrosis Neonatal Screening Group

1 Wald NJ, Morris JK. Neonatal screening for cystic fibrosis. *BMJ* 1998;316:404-5. (7 February 1998.)
2 Farrell PM, Kosorok MR, Laxova A, Shen G, Koscik RE, Bruns T, et al. Nutritional benefits of neonatal screening for cystic fibrosis. *N Engl J Med* 1997;337:963-9.
3 Baroni MA, Anderson YE, Mischler EH. Cystic fibrosis newborn screening: impact on early screening results on parenting stress. *Pediatr Nurs* 1997;23:143-51.
4 Farrell PM, Shen G, Splaingard M, Colby CE, Laxova A, Kosorok MR, et al. Acquisition of Pseudomonas aeruginosa in children with cystic fibrosis. *Pediatrics* 1997;100:e2. Available from http://www.pediatrics.org/.
5 Mischler EH, Wilfond BS, Fost N, Laxova A, Reiser C, Sauer CM, et al. Cystic fibrosis newborn screening: impact on reproductive decision making and implications for genetic counseling. *Pediatrics* 1998;102:44-52.

Smoking and risk of myocardial infarction

Statistical and biological interactions should not be confused

EDITOR—Prescott et al report that smoking increases the risk of myocardial infarction significantly more in women (relative risk 2.24) than in men (relative risk 1.43).[1] Interactions between components of smoke and hormonal factors were suspected.

Readers may conclude from this study that men and women do not differ at all. On the basis of data on the prevalence of smoking (table 2 in Prescott et al's paper) and from reported relative risks, we can calculate that in women the risk of developing myocardial infarction during follow up is 5.88% (380/6461) in smokers and 2.63% (132/5011) in non-smokers; in men, the risk is 10.62% (902/8490) in smokers and 7.38% (349/4701) in non-smokers. These are best estimates based on published data; the figures would change slightly if former smokers were removed from the group of non-smokers. The difference that is attributable to smoking was therefore 3.25% in women and 3.24% in men. Over 12 years, smoking caused an additional myocardial infarction in one person out of 31—equally distributed between men and women.

This shows that statistical interaction should not be confused with biological interaction. Statistical interaction concerns the modelling of combined effects of two or more risk factors for a disease in populations, and biological interaction refers to biochemical reactions in an individual. Whether statistical interaction exists or not depends on the specification of the model that is applied to data—"interaction" means that a model that simply adds the effects of two risk factors (in this case sex and smoking) does not accurately describe their joint effect (the risk of myocardial infarction in men who smoke).

Prescott et al used a multiplicative model and found a significant interaction; I used an additive model and found none. It is not uncommon to find a positive interaction on the additive scale and a negative interaction on the multiplicative scale. Models of absolute and relative risk have their respective merits and disadvantages, neither is wrong or right, and neither has anything to say about the biology of the phenomenon under study. Prescott et al may be right in their hypothesis that components of smoke interact with hormones in causing myocardial infarction, but their data do not show that this is happening.

Thomas V Perneger *Medical epidemiologist*
Institute of Social and Preventive Medicine, University of Geneva, CH-1211 Geneva 4, Switzerland

1 Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. *BMJ* 1998;316:1043-7. (4 April.)

Studying relative risk is not enough

EDITOR—Prescott et al show that women who smoke have a high relative risk of myocardial infarction, which is highest in those aged under 55 and decreases with age.[1] These age specific relative risks are higher than those for men at the same age. Prescott et al hypothesise that tobacco may be more harmful to women because of antioestrogenic effects. The greater risks in women and young people could, however, have alternative explanations.

As in all other populations studied, the absolute risk is much less in women than in men and in young than in old people, as Prescott et al show in their figure 1.[1] The additional absolute risk caused by smoking is small among young women and relatively high only because of the low baseline level. Should Prescott et al rather suggest that smoking is less harmful in women?

Relative risk measures the effect of a risk factor for a disease compared with the total effects of all other risk factors for the same disease in a population. A greater relative risk may simply be a result of studying a population that has few other risk factors for the disease.[2] It is a misinterpretation of heterogeneity of relative risk to consider a greater relative risk to be more harmful when its absolute clinical and public health impact is small and more appropriately measured by attributable risk.[3] The relative risk due to smoking, for example, is much higher for lung cancer than heart disease—lung cancer has few other causes, but smoking kills more people through heart disease because this disease is much more common, so the additional absolute risk (the attributable risk) of heart disease is much greater. Epidemiological studies show that the relative risk of raised blood pressure and raised blood cholesterol concentrations is much greater in young people than in middle aged or elderly ones. Does this mean that these factors are more harmful in young people? Clinical and preventive measures have generally been targeted at older people as the benefits from intervention in young people are too small to be worth while.

The greater relative risk that Prescott et al observe in women is due only to the fact that women before the menopause have much fewer or lower levels of risk factors than men of the same age. To postulate a new effect is not warranted on the basis of these data.

Jin-Ling Tang *Associate professor in community medicine*
James A Dickinson *Professor of family medicine*
Department of Community and Family Medicine, Chinese University of Hong Kong, Hong Kong

1 Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. *BMJ* 1998;316:1043-6. (4 April.)
2 Rothman K, Poole C. A strengthening programme for weak associations. *Int J Epidemiol* 1968;17(suppl):955-9.
3 Greenland S, Rothman KJ. Concepts of interaction. In: Rothman KJ, Greenland S, eds. *Modern epidemiology.* 2nd ed. Philadelphia: Lippincott-Raven;1998:329-42.

Smoking is a feminist issue

EDITOR—Prescott et al's finding that women who smoke are at 50% greater risk of myocardial infarction than men who smoke is important and deserves wide publicity.[1] Cardiovascular disease is, however, not the only risk associated with smoking. There is already strong evidence that smoking is 20-70% more likely to result in lung cancer in women than in men,[2] and the risk of oral cancer is more than doubled in women.[3] Although lung cancer has recently overtaken breast cancer as the commonest cause of death from cancer in British women, the epidemic of smoking related deaths in women is only just beginning.

Prescott et al comment that the excess risk of death from cardiovascular disease falls rapidly when people stop smoking. The same is not true for lung cancer, where the risk falls slowly. Smoking causes clonal mutations in the respiratory epithelium that persist for years.[4 5] Consistent with this, smoking in youth is more dangerous than smoking in old age.

Women know that they are more susceptible to alcohol than men. They need to learn that they are also at greater risk from smoking than men. On a visit to the United States last month I was horrified to see one brand of cigarettes advertised on billboards as "a woman thing." The cynical marketing of cigarettes to women in developing countries will ensure that the lessons so painfully learnt here are repeated thoughout the world.

Penella J Woll *Senior lecturer*
Department of Clinical Oncology, Nottingham City Hospital, Nottingham NG5 1PB

1 Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. *BMJ* 1998;316:1043-6. (4 April.)
2 Zang EA, Wynder EL. Differences in lung cancer risk between women and men: examination of the evidence. *J Natl Cancer Inst* 1996;88:183-92.
3 Muscat JE, Richie JP, Thompson S, Wynder EL. Gender differences in smoking and risk for oral cancer. *Cancer Res* 1996;56:5192-7.
4 Mao L, Lee JS, Kurie JM, Fan YH, Lippman SM, Lee JJ, et al. Clonal genetic alterations in the lungs of current and former smokers. *J Natl Cancer Inst* 1997;89:857-62.
5 Wistuba I, Lam S, Behrens C, Virmani AK, Fong KM, LeRiche J, et al. Molecular damage in the bronchial epithelium of current and former smokers. *J Natl Cancer Inst* 1997;89:1366-73.

Authors' reply

EDITOR—We do not agree with Perneger et al that statistical interaction and biological interaction are separate issues. Statistical interaction depends on specification of the model that is applied to data. Epidemiological analysis, however, usually attempts to go beyond statistical modelling,[1] and, provided the model fits the data, statistical interaction may well have a biological interpretation.

When we found a statistical interaction between smoking and subjects' sex we wondered whether this was a result of our fitting a multiplicative model on data that should be described in an additive model. We discussed this in our paper. We find it biologically plausible that cardiovascular risk factors should act in a multiplicative fashion. If, however, effects of risk factors are additive, relative risks from a multiplicative model will vary between men and women simply because baseline risks vary. If this was the case we would, firstly, expect to find higher relative risks in women for all of the cardiovascular risk factors studied (cholesterol concentration, blood pressure, body mass index, physical activity, etc). Relative risks for all of these risk factors were, however, similar in men and women. Secondly, we would expect the sex difference—the interaction term—to diminish with increasing age since baseline risks increase. This was also not found. From this we cautiously suggested possible differences in the mechanisms of action of tobacco in causing cardiovascular disease in men and women.

Our calculation was based on an additive model that was briefly described in the paper. We calculated the difference in risk—number of additional myocardial infarctions in smokers caused by smoking—on the basis of age specific relative risks for smoking and baseline incidence. We concluded that the difference in risk was higher in men up to age 65 and in women over age 65. The model suggested by Perneger et al cannot pass as an additive model. It ignores age, time under risk, and the fact that the female smokers in our study population were on average much younger than the female non-smokers.

Finally, it is important to recognise that from a public health point of view the relative risk associated with smoking is higher in women, since calculations of the impact of smoking on women's health should not be based on relative risks calculated from studies of men.

Eva Prescott *Senior research fellow*
Merete Hippe *Research fellow*
Institute of Preventive Medicine, Kommunehospitalet, DK-1499 Copenhagen K, Denmark

1 Rothman KJ. Interactions between causes. In: Rothman KJ. *Modern epidemiology.* Boston, MA: Little, Brown; 1986: 311-26.

Advice to authors

We prefer to receive all responses electronically, sent either directly to our website or to the editorial office as email or on a disk. Processing your letter will be delayed unless it arrives in an electronic form.

We are now posting all direct submissions to our website within 72 hours of receipt and our intention is to post all other electronic submissions there as well. All responses will be eligible for publication in the paper journal.

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

Please supply each author's current appointment and full address, and a phone or fax number or email address for the corresponding author. We ask authors to declare any competing interest.

Letters will be edited and may be shortened.

www.bmj.com
letters@bmj.com