Letters

Save European research campaign

See editorial by Woods

EDITOR—The Save European Science campaign (www.SaveEuropeanResearch.org) was launched on 9 December 2003 out of concern for the future of academic and investigator led research in Europe with the advent of the European Union clinical trials directive (see p 240). It was launched from a cancer platform but is inclusive in spirit and has already gained momentum in cardiology, dermatology, and psychiatry.

The directive was written and passed after minimal consultation with interested parties in the member states. Frustration at the inevitability of its arrival in May 2004 and the lack of a process to alter its course was much discussed at medical conferences and meetings around the world last year. This concern is reflected in the fervour with which researchers from all over Europe and the world have signed the letter to MEPs on the campaign's website. It starts, "why did the European Union decide to stop cancer research," and by 15 January more than 2000 researchers had signed.

The directive raises the bar in terms of quality and reporting standards for all research. The pharmaceutical industry has understandably accepted this as an achievable minor inconvenience. What is new is that this is now the minimum standard for all clinical research regardless of the financial backing or goal of the project. Under the directive all investigators must take on more paperwork, liability, reporting, and cost burden.

Little was wrong with the processes of academic or investigator led research in the European Union in the first place. Many important medical breakthroughs in recent times have been a product of this mechanism. Several eminent American and Australasian researchers have signed the letter, with messages of support that they consider it bad news for the development of medicine if European academia is shut out.

To be updated on the progress of this campaign, please sign the letter and provide an email address to receive regular reports.

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Competing interests: None declared.

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Quality of randomised controlled trials

Quality of trial methods is not good in all disciplines

EDITOR—The paper by Soares et al is a useful reminder of the important distinction between quality of trial reporting and quality of trial methods.[1]

An established, motivated, and informed group such as the Radiation Therapy Oncology Group is likely not only to have well designed trials but to conduct them according to the protocol. Soares et al show that omission of important information in the trial reports of such a group can now be looked at more benevolently.

It is too large a leap of faith to extend this to other areas—for example, to small, often dated, suboptimal, underfunded trials. My experience in chasing up further information for trials in orthopaedics has yielded mixed and often disappointing results. Tracking down the trial investigator(s) has been difficult. Of those who could be found and replied, few were able to give completely satisfactory replies, sometimes because they no longer had access to documentation, even for comparatively recent trials.

Allocation concealment is a prime measure of trial quality and often used to select studies for systematic reviews. Allocation concealment was achieved in all trials conducted by the Radiation Therapy Oncology Group, despite being reported in only 42% of its papers.[1] However, in our Cochrane review of eight trials of preoperative traction for hip fracture, further information on the method of randomisation was received for four of the six trials whose reports had not adequately described the method of randomisation.[2] Allocation was concealed in one trial but another was quasi-randomised; information on the other two trials remained insufficient to make a judgment.

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Competing interests: None declared.

1 Soares HP, Daniels S, Kumar A, Clarke M, Scott C, Swann S, et al. Bad reporting does not mean bad methods for randomised trials: observational study of randomised controlled trials performed by the Radiation Therapy Oncology Group. *BMJ* 2004;328:22-4. (3 January.)
2 Parker MJ, Handoll HHG. Pre-operative traction for fractures of the proximal femur. *Cochrane Database Syst Rev* 2003;(3):CD000168.

Quality of research may be worse than it appears

EDITOR—del Giglio and Costa argue that the quality of randomised controlled trials may be better than assumed.[1] Some articles do not present full details of the study they report and are rated by reviewers below their value. But authors of many articles try to beautify their reports by omission of non-attractive details and by other means.

Because clinical medicine is on the side of the patient or consumer, in cases that are not clear it will be safer to rely only on what is clearly said in a report. We must be critical when reading articles, because we often hear about falsification of research data. As a reviewer I know how difficult it is to receive additional details of a study from authors, and it is naive to think that matters will improve greatly in the near future.

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1 Del Giglio A, Costa LJ. The quality of randomised controlled trials may be better than assumed. *BMJ* 2004;328:24-5. (3 January.)

Caution is important

EDITOR—I agree with Vlassov's comments on the paper by del Giglio and Costa (previous letter).[1] Research articles must be read with a critical eye, and it should not be assumed that high quality methods have been followed.

To assume that the protocol for a trial was followed exactly is dangerous, especially when the report does not reflect this. At what point does the assumption of good quality stop? It is often said that critical appraisals of articles are performed blinded to the authors, their institutions, and the publisher so that the report is read purely for its own merit.

I am also concerned that reviewers should contact trialists for original protocols. Although this is always good practice to clarify any uncertainities, it is time consuming and costly. The grants available for systematic reviews and meta-analyses do not

tend to include enough money or time to make this a practical solution to the problem. Instead, the emphasis should be placed on high quality reporting so that all of the pertinent information is placed accurately in the report. This is the most practical way of making systematic reviews feasible and accurate.

These opinions are NB's and not do not necessarily reflect those of the organisation for which she works.

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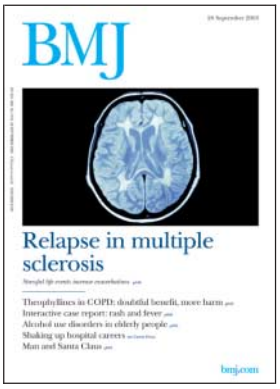
1 Del Giglio A, Costa LJ. The quality of randomised controlled trials may be better than assumed. *BMJ* 2004;328:24-5. (3 January.)

Stress and exacerbations in multiple sclerosis

Whether stress triggers relapses remains a conundrum

Editor—The front page of the *BMJ* of 20 September 2003 carries the title: "Relapse in multiple sclerosis: stressful life events increase exacerbations." Buljevac et al present evidence that psychological stress is associated with a doubling in risk of relapse.[1] Two issues arise.

Firstly, this study has limitations, some of which are clearly acknowledged by the authors. The most critical limitation of the study is recall bias. Patients having a relapse are more likely to seek an explanation and hence report stressful events during preceding weeks. In other diseases such as myocardial infarction, patients commonly attribute their illnesses to psychological factors.[2]



Secondly, association does not equate to causality. An alternative hypothesis is that "psychological stress" and neurological relapse are different temporally disseminated manifestations of the same underlying disease process. Magnetisation transfer changes precede the traditional radiological signs accompanying clinically overt neurological relapse by up to three months.[3] Subclinical reversible cognitive changes accompany relapses.[4]

Thus an appreciable number of negative life events could have occurred, or be perceived to have occurred, as a result of subtle changes in cognition or behaviour preceding an overt clinical relapse. Several groups have reported the presence of an association between relapse and mild to moderate stressful life events (which might occur secondary to changes in daily life management). This association disappears with major negative life events (which are beyond control).[5] Since disease burden was not controlled for, we do not know whether stressful life events predicted relapse independently of what may have also elicited such events.

The study's impact on the understanding of relapse pathogenesis needs to be assessed with caution.

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1 Buljevac D, Hop WC, Reedeker W, Janssens AC, van der Meche FG, van Doorn PA, et al. Self reported stressful life events and exacerbations in multiple sclerosis: prospective study. *BMJ* 2003;327:646. (20 September.)
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3 Filippi M, Rocca MA, Martino G, Horsfield MA, Comi G. Magnetization transfer changes in the normal appearing white matter precede the appearance of enhancing lesions in patients with multiple sclerosis. *Ann Neurol* 1998;43:809-14.
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Authors' reply

Editor—We agree with Galea et al that recall bias could be an alternative explanation for our finding that stressful events are associated with the risk of exacerbation in multiple sclerosis.

To minimise the possibility of recall bias we chose a high (weekly) sampling frequency. Nevertheless, when patients experienced an event and still had to complete the questions for the preceding week, their perception of stress may have been influenced by the relapse. In such a situation a high frequency of stress within or just before the week of the relapse would also be expected. This was not the case in our study: we found no significant increase in the number of reported stress events two weeks before an exacerbation.

Galea et al are right that increases in stressful events preceding exacerbations do not directly prove a causal relation—we do not claim that. They suggest that subclinical disease processes may underlie the experience of stress in the weeks before the onset of a relapse. In that case, the experience of stress does not precede exacerbations but is the consequence of subclinical disease activity.

The occurrence of events that are not related to multiple sclerosis is independent of subclinical disease processes, but patients may experience these as more stressful when they do not feel well. Yet, if this were true, one would also expect heightened report of stress at the time of infections. We did not find evidence for a relation between stress report and clinically manifest infections. These findings argue against the possibility of experiencing stress as a consequence of subclinical disease activity.

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WHO's world health report 2003

Actions speak louder than words

Editor—Walt's editorial on the *World Health Report 2003* highlights the challenges of health and inequality.[1] The report makes grim reading and shows the failure of past initiatives.[2] It has taken the world 25 years to realise the importance of strengthening health systems and developing primary health care. The return to the Alma Ata declaration of 1978 may be welcome, but whether its pronouncements and initiatives are more than just rhetoric and slogans remains to be shown.

Despite the failure of most of its previous targets, such as health for all, and specific disease eradication initiatives, such as malaria, tuberculosis, kala azar, etc, the report is still setting up new targets—for example, giving 3 million people antiretroviral treatment by 2005.[2] The health parity cannot be achieved by isolated specific disease initiatives without strengthening health systems, alleviating poverty, and improving infrastructure.

Poverty is strongly correlated with ill health. About 1300 million people (20% of the world's population) live in absolute poverty. HIV/AIDS, malaria, tuberculosis, diarrhoeal diseases, malnutrition, maternal mortality, and child mortality all disproportionately affect poor people (WHO Regional Office for the Western Pacific, conference, Manila, September 2000). As many as 1.1 billion people have no access to clean water, and 2.4 billion have inadequate sanitation; 2 million still die every year from water related illnesses.[3] Can health be improved without providing basic amenities such as clean water and sanitation?

Poor health retains people in poverty, and poverty keeps them in poor health.[4] To break

this vicious circle and liberate the poor from poverty and ill health we need more meaningful and effective programmes.

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Competing interests: None declared.

1 Walt G. WHO's world health report 2003. *BMJ* 2004;328:6. (3 January.)
2 World Health Organization. *World health report 2003.* Geneva: WHO, 2003.
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Time to ease the mental health burden

Editor—The World Health Organization in its *World Health Report 2003* depicts graphically, in table 1.2, that the leading cause of disease burden for women aged 15 years and older worldwide in 2002 was unipolar depressive disorder.[1 2] For men, the fourth, seventh, and eighth positions concerned mental health.

The inference from these data is obvious: mental health is in terrible shape. What amazes me is that easing the mental health burden is not even referred to tangentially.

Didn't the WHO at its very inception define health "as a state of complete physical and mental wellbeing" and then declare it a fundamental human right?

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2 World Health Organization. *World health report 2003.* Geneva: WHO, 2003.

Special issue on South Asia

Health economics is neglected in this region

Editor—A special issue on South Asia is welcome.[1] The region provides ample opportunity for the world to discuss and learn from its problems and experiences. Yet little is known about its disease burden and barriers to health care as researchers either do not exist or do not get published. As a result, international estimates, such as disability adjusted life years, for this region could be faulty. Resource allocation based on such estimates could put the region at a loss. Besides, there are emerging issues such as health inequity, government withdrawal from health care, lack of insurance, and cost ineffective use of resources.

However, this region is not just full of problems. New practices are emerging that could serve as models to the rest of the world. Kerala's model of "good health at low cost" is well known; other models are adoption of government healthcare institutions by industry, non-governmental organisations, or local self government and Tamil Nadu's model of drug distribution to government institutions (D Varatharajan, international conference on unity in education, training and healthcare delivery, Newcastle, October 2003). Strong, efficient, and equitable government healthcare provision is one of the basic requirements of good health at low cost.[2]

Health economics research has been neglected in this region and deserves space in the special issue.

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Competing interests: None declared.

1 Bhutta Z, Nundy S, Abbasi K. Why a special issue of the *BMJ* on South Asia? *BMJ* 2003; 327: 941-2. (25 October.)
2 Kishnan TN. Access and the burden of treatment: An inter-state comparison. Thiruvananthapuram: Centre for Development Studies, 1994. (Studies on human development in India, discussion paper No 2.)

Focus will be an eye opener

Editor—Bhutta et al discuss the reasons for publishing a special issue on South Asia.[1] I believe that participating in global health is an extension of our responsibility as doctors to serve humanity.

Nepal's total health expenditure per capita is $66.[2] It lacks adequately trained healthcare staff, infrastructure, and planning that can support the healthcare needs of a fundamentally unique and geographically distinct group of people, especially women and children. At the crux of the problem lies illiteracy and ignorance combined with a lack of vision from the top.

The *BMJ*s focus on South Asia should be an eye opener for healthcare professionals, policy makers, and the people at large.

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1 Bhutta Z, Nundy S, Abbasi K. Why a special issue of the *BMJ* on South Asia? *BMJ* 2003;327:941-2. (25 October.)
2 World Health Organization. *Nepal.* www.who.int/country/npl/en/ (accessed 16 Jan 2004).

Colchicine in acute gout

Optimal dose of colchicine is still elusive

Editor—Morris et al discussed the use of low dose colchicine in gout.[1] The treatment dose of colchicine, which has remained at 1 mg initially, followed by 500 µg every 2-3 hours for many years, should be reviewed. However, they are incorrect to say that the current *BNF* (*British National Formulary*) recommends a regimen for colchicine that is unchanged since the 1966 edition.

In September 1999 the *BNF* reduced the total dose of a course of colchicine from 10 mg to 6 mg.[2] Before 1981 the *BNF* did not even state the higher limit of 10 mg.

The decision to reduce the total dose of colchichine to 6 mg was taken because of expert advice given to the *BNF*.[3] The formulary committee reported that it found little evidence to support the use of the total dose of 10 mg and that a total dose of 6 mg has been recommended in the United States.[4]

After nearly 2000 years of recorded use of colchicine we are still struggling to find its optimal dose. Recent history seems to be one of a gradual reduction in the total dose. Morris et al, by suggesting a reduction in dose frequency, may reduce further the unpleasant adverse effects of this useful agent.

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Competing interests: None declared.

1 Morris I, Varughese G, Mattingly P, Colchicine in acute gout, *BMJ* 2003;327:1275-6. (29 November.)
2 Joint Formulary Committee. *British national formulary.* London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 1999. (No 38.)
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4 Martindale: *The complete drug reference.* 32nd ed. London: Pharmaceutical Press, 1999.

Low dose colchicine was started after usual dose

Editor—Morris et al emphasise that in acute gout lower doses of colchicine are effective yet less toxic than traditional regimens.[1] Certain points need, however, to be considered.

In all the three cases quoted the patients initially started taking higher (traditional) doses of colchicine and only after they had experienced adverse effects were their doses reduced. This means a lingering effect of colchicine would be present. Evidence shows that colchicine will be present in leucocytes (site of action) for at least nine days after a single intravenous dose.[2] To claim that a lower dose of colchicine is effective, should one not start with a lower dose?

Because toxicity is more common with colchicine, non-steroidal anti-inflammatory drugs (NSAIDs, such as indomethacin or naproxen) are preferred.[2] In one of the three cases mentioned, meloxicam was tried without benefit. Meloxicam is a drug with a long half life, and it needs time for steady state concentration to be achieved.

Colchicine has generally been replaced by less toxic drugs such as NSAIDs,[3 4] and corticosteroids (preferably via intrasynovial injection)[3] for relief of an acute attack. Colchicine should be reserved for patients in whom these other agents are contraindicated or ineffective.[3] Although Morris et al claim that they do not advocate an increase in the use of colchicines, it seems that all other avenues were not exhausted. Colchicine has been reported to be equally effective, and the gastrointestinal side effects

may be avoided almost completely if it is given intravenously.[2]

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1 Morris I, Varughese G, Mattingly P, Colchicine in acute gout, *BMJ* 2003;327:1275-6. (29 November.)
2 Roberts II LJ, Morrow JD In: Goodman and Gilman's *The pharmacological basis of therapeutics*. 10th ed. New York: McGraw Hill, 2001:687-731
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4 Roberts WN, Liang MH, Stern SH. Colchicine in acute gout. Reassessment of risks and benefits. *JAMA* 1987;257:1920-2.

Authors' reply

EDITOR—Cox rightly points out that a total dose of colchicine has been introduced to advice in the *BNF* (*British National Formulary*) in recent years and is now at a 6 mg limit. The advice that has not changed is the traditional high dose regimen of 1 mg, followed every two hours by 0.5 mg, until relief of pain is obtained or vomiting or diarrhoea occurs.[1]

In Ahern et al's study all patients given high dose colchicine developed diarrhoea or nausea in 12-36 hours with a mean dose of 6.7 mg[2]; many patients taking high doses who have been referred to us have gastrointestinal adverse effects below a total dose of 6 mg. We find that the total dose is not really relevant for acute situations with the low dose regimen.

Sivagnanam wonders if our patients settled because of the residual effect of the previously administered high dose colchicine that we had stopped; we only reintroduced colchicine, however, if the gout was not settling or was worsening. We have treated other patients with acute gout by using low dose colchicine from the beginning, and symptoms in these patients settled promptly and without adverse event.

Whether non-steroidal anti-inflammatory drugs (NSAIDs) are less toxic than colchicine is debatable, particularly compared with low dose colchicine. Normally we use NSAIDs first unless there are contraindications or adverse events, as seen in our cases. Intrasynovial steroids are not always practicable.

We cannot recommend intravenous colchicine and agree with Pawlotsky that although highly effective it should no longer be used, because of local and general complications associated with a risk of death.[3]

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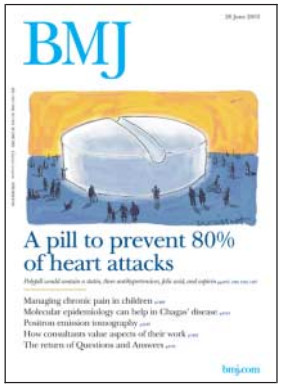
1 Joint Formulary Committee. *British national formulary*. London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 2003;(46):497.
2 Ahern MJ, Reid C, Gordon TP, McCredie M, Brooks PM, Jones M. Does colchicine work? The results of the first controlled study in acute gout. *Aust N Z J Med* 1987;17:301-4.
3 Pawlotsky Y. Treatment of gout. *Rheumatol Eur* 1996;25:142-4.

Polypill debate continues

Concept is a fascinating thought experiment

EDITOR—The Polypill concept is dependent on two huge assumptions—that it will reduce cardiovascular events by a large amount and that it will prove so safe that routine surveillance is unnecessary.[1] But the serious possibility that both are true provides a fascinating thought experiment.

To benefit from the Polypill you would not need to be a patient (any more than you now need to be a patient to take a walk or drink wine). You would not need a doctor, a nurse, checks, or records. You would not need to know whether you are specially at risk, and neither would your insurance company nor your employer. You would not need to be labelled, admonished, praised, patronised, or worried or, conversely, led into orgies of life threatening celebration. And the government would have nothing to do with the matter at all.



It is not at all clear whether the government wants people in general to live a decade longer, and it is not at all clear whether people in general want to live that much longer either. It will be interesting to see whether our rulers, eager in the past to appear good doctors, decide to explore making such potentially enormous benefits available by sponsoring the necessary research, which will not be done spontaneously by a pharmaceutical industry with nothing to gain and much to lose by a positive outcome. Or perhaps they are going to quietly let the idea (and us) die the death.

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Competing interests: None declared.

1 Editor's choice. Polypill may be available in two years. *BMJ* 2003;327:0. (4 October.)

People will always be sceptical

EDITOR—After reading some of the responses to Wald and Law's findings I find Smith's term "medical conservatism" well chosen.[1 2] Sarcastic remarks and side swipes are part of life; as we say in German: "The dogs howl, but the moon still keeps on shining." In every great push forward there will be some people who don't think it is a good direction and will start criticising.

The health of millions is at stake, and new, especially cost efficient, approaches are clearly needed. As a medical student I can't look back on many years of experience, but I do want to look forward to getting a grip on the main killers in our society one by one, of which cardiovascular disease is a prominent one. Taking a polypill a day won't take the place of a healthy lifestyle, but it may help weaken one of mankind's great foes.

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1 Editor's choice. Polypill may be available in two years. *BMJ* 2003;327:0. (4 October.)
2 Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;326:1419-24.

Similar combination of drugs has worked in natural experiment

EDITOR—Forty five years ago I sustained a whiplash injury to my neck. I appeared before an industrial injuries board, where I was fully examined, and so was fortuitously found to have a blood pressure of 260/140. I treated myself over the following years with increasingly effective antihypertensive drugs and so have now been taking drugs similar to those in the Polypill for many years.[1] The only drug I have omitted is aspirin, as this has caused repeated haemorrhages.

I believe that the damage to the endothelial wall of the coronary and cerebral blood vessels is caused by repeated fluctuating hypertensive filling in usually normotensive or hypertensive patients, and that sustained hypertension is less dangerous.[2] The fluctuating hypertension causes the damage to the arterial wall and leads to platelet aggregation and subsequent thrombosis and occlusion of the blood vessel. If the fluctuation can be diminished the likelihood of damage to the endothelium is less.

I have therefore been on a "Polypill" more or less for over 45 years. I am now 90 years old, very active, in full possession of my mental faculties, physically strong, and fortunately have had no vascular accident of any sort. Can anybody doubt that this fortunate result is due to this drug treatment? A man of 45 with a blood pressure of 260/140 would certainly not expect to reach my current age, and I found it very rewarding to read now that my prognostication 45 years ago seems to have been along the right lines.

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Competing interests: None declared.

1 Editor's choice. Polypill may be available in two years. *BMJ* 2003;327:0. (4 October.)
2 Frankel E. Coronary disease and personality. *BMJ* 1969;i:382-3.