CORRESPONDENCE

e-mail submissions to correspondence@lancet.com

Screening for breast cancer with mammography

Sir—I am concerned about some features of Ole Olsen and Peter Gøtzsche's review (Oct 20, p 1340).[1] I refer especially to their comments on systematic reviews of causes of death, as applied by the investigators of the Health Insurance Plan (HIP) trial,[2] and later adapted to the Canadian National Breast Screening study (CNBSS)[3] and other trials.[4]

I was one of the death reviewers for the HIP trial, initiated the death review in the CNBSS, and I chair the Death Review Committee for the Prostate Lung Colon and Ovary trial (PLCO).[4]

The HIP trial was done in an era when the size of breast cancers was much larger than became usual in the subsequent two decades in North America. I recall no instance in which the masking of the allocation was compromised. The major difficulty for the reviewers was not whether the patient died of cancer, nor whether breast cancer had been diagnosed, but whether breast cancer was the cause of death when the patient had been diagnosed with another malignant disease. The decisions made were entirely masked, even after consultation between the reviewers for initial disagreement.

Lumpectomy was not practised, although radiotherapy was used frequently, especially for locally advanced disease. However, if an unrecognised consequence of radiotherapy was the cause of death, and was labelled as cardiovascular disease, such labelling would have been applied without bias as to treatment assignment.

Olsen and Gøtzsche comment that equal numbers of patients, by allocation, were reviewed, but that the numbers assigned to breast cancer as a cause of death were fewer in the screening group, and they cite this as evidence of bias. An alternative explanation is more plausible. If screening was truly effective, then the numbers of deaths from breast cancer in a reviewed series would be less in the screened group. It seems not to have occurred to Olsen and Gøtzsche that the equal numbers reviewed could have resulted from a deliberate attempt to ensure that equivalent numbers of patients in the two groups were reviewed at the same time to avoid bias.

I am also concerned by Olsen and Gøtzsche's comments on the difference in numbers of women with breast cancer excluded from the two groups. This difference arose because, when women in the screened group attended for screening, previously diagnosed breast cancers were identified, but this was not possible for the controls. The 18-year follow-up, however, enabled all deaths from breast cancer to be identified in the two groups; identification of the date of diagnosis was then possible from hospital records. Patients diagnosed before randomisation were excluded.[2] Although this process did not eliminate the inequality in the numbers of patients with previously diagnosed breast cancers still living at 18 years who were not excluded, the small difference in person-years of observation is unlikely to have biased the results.

Therefore I believe the HIP trial results are valid, and the trial should not be dismissed as flawed.

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1 Olsen O, Gøtzsche PC. Cochrane review on screening for breast cancer with mammography. *Lancet* 2001; **358:** 1340–42.
2 Shapiro S, Venet W, Strax P, Venet L. Periodic screening for breast cancer: the Health Insurance Plan Project, 1963–1986, and its sequelae. Baltimore: Johns Hopkins University Press, 1988.
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Sir—Ole Olsen and Peter Gøtzsche's review[1] concurs with the findings of their earlier report[2] that screening mammography programmes do not reduce breast-cancer mortality and lead to more aggressive treatment. In his Oct 20 Commentary, Richard Horton[3] agrees with their conclusion that screening mammography programmes are not therefore justified. These conclusions could have a major effect on women's health care and deserve careful scrutiny.

Our primary criticism is the notion that a screening programme can be justified only if it reduces mortality. Mortality is a very important outcome, and easily measured, and choosing an outcome parameter for ease of measurement is a common bias among clinical investigators. However, outcomes such as quality of life are also important to patients and could justify screening programmes. Unfortunately, such outcomes have been understudied in the assessment of breast-cancer screening. Rather than making assumptions about whether false-positive tests and earlier detection of breast cancer improves or harms quality of life, objective measurement is needed of how mammography screening programmes affect quality of life, and whether certain types of patients will benefit more than others.

Olsen and Gøtzsche conclude that screening mammography leads to overly aggressive treatment. If that is true, it is a condemnation of treatment practices, not of screening. Our organisation is one of many encouraging better education of patients and physicians to lower the prevalence of unnecessarily aggressive treatment. The best solution to improving treatment is better technology, education, and training, along with improved communication between physicians and patients. These strategies deserve more attention from the medical community before a decision is made to eliminate screening programmes that lead to earlier diagnoses. There is no need to throw out the baby with the bath water.

We are also concerned with the meta-analysis itself. In six of seven randomised trials (including the extended Malmö trial[4]) analysed by Olsen and Gøtzsche, a reduction in breast-cancer mortality was associated with the use of screening mammography. We recommend caution before rejecting these findings, which incorporated data from hundreds of thousands of patients, on the basis of one meta-analysis.

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Meta-analysis requires many subjective decisions on the selection and weighting of variables. Each decision can introduce bias, no matter how systematic the decision-making process. A second set of investigators carefully analysing the same data might reach very different conclusions. For example, many investigators did not agree with Olsen and Gøtzsche's decision to deem certain clinical trials unreliable on the basis of small baseline differences in mean age between screening and control groups.[5]

Meta-analyses are an evolutionary improvement over the traditional review article, but their limitations must be acknowledged before they are used to formulate major health-policy decisions. The attention garnered by Olsen and Gøtzsche illustrates the need to assess each meta-analysis thoroughly, as well as to reassess the proper role of meta-analyses.

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5 Hayes C, Fitzpatrick P, Daly L, Buttimer J. Screening mammography re-evaluated. *Lancet* 2000; **355:** 749.

Sir—In their overview of breast-cancer screening, Ole Olsen and Peter Gøtzsche[1] claim that the main reason for the continuing controversy about their analysis of imbalances in baseline variables is that their opponents keep referring to the criticisms of their paper without referring to their reply. On the contrary, their replies have contained nothing worth referring to.[2,3]

Olsen and Gøtzsche do not address the original criticism of their study, which is the real problem. This inaction is a shame, because some other points they make are reasonable and, in view of the uncritical acceptance of the value of screening by politicians, the case against is worth making.

We have previously pointed out to Olsen and Gøtzsche that cluster-randomised trials will be expected to show greater variability in balance at baseline than trials randomised at patient level.[4] This variability is not a problem provided that such trials are analysed properly. The Cochrane Collaboration's favourite tool, RevMan, can analyse only single-centre parallel-group trials with no covariates, and, therefore, their researchers are apt to see any other sort of trial as problematic. This problem should not be inflicted on a research community that is not limited to primitive analysis.

I believe Olsen and Gøtzsche's previous criticisms about randomisation have been irrelevant and unfair. For example, the Edinburgh randomised trial of breast cancer[5] allowed for cluster randomisation, which RevMan cannot do. Two of that study's coauthors were, however, statisticians well known for their expertise in mixed-effect models. Whatever other features of Olsen and Gøtzsche's criticism are valid, the way they have used baseline tests of covariate balance on cluster-randomised trials is not.

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2 Gøtzsche PC, Olsen O. Screening mammography re-evaluated. *Lancet* 2000; **355:** 752.
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Sir—Predictably, Ole Olsen and Peter Gøtzsche's conclusion[1] that mammographic screening is of uncertain benefit and leads to greater use of more aggressive treatment and other harms, has provoked adverse criticism from many who believe that screening saves lives. Richard Horton, in his Commentary,[2] and the alternative version of the report on the journal's internet site[3] have exposed disagreement among the editorial ranks of the people responsible for producing Cochrane systematic reviews of evidence for breast cancer: this is a problem of serious import.

The new elements in this latest review that confirm and strengthen Olsen and Gøtzsche's previous findings, rest on their statement that breast cancer mortality is a misleading outcome measure. It is occasioned by their findings that mammographic screening leads to greater use of more aggressive treatment, increases the number of mastectomies by about 20%, and inflicts important psychological distress on more than 10% of the healthy population who attend screening programmes, evidenced in a cited systematic review.

These arguments have been in the public domain for some time,[4] but are largely dismissed as irrelevant by workers zealously pursuing the goal of reduction of mortality from breast cancer, without regard for the risks, limitations, and consequences, to women invited for screening but not informed about the risk of the procedure or of receiving a diagnosis of ductal carcinoma in situ.

Olsen and Gøtzsche point out that mass screening involves the entire population and may cause a screening-associated increase in mortality, as well as other harms.

Attempts by the Cochrane Breast Cancer Review Group to suppress these features, by insistence on changes to the review as a condition of its publication in the *Cochrane Library*, are a blatant threat to the over-riding principle of freedom of appointed investigators to place all legitimate findings in the public domain without judgmental interference.

Such threats to integrity must not be allowed to go unchallenged. Attempts to muzzle unpopular findings, if successful, would undermine trust in research processes and methods to the harm of the general welfare of society and progress in health care. The gate-keeping function of medical journalism has again been put to the test.[5] Preservation of freedom of speech is essential so that careful reflection and proper discussion may follow, because the implications for women and policy makers are substantial.[2]

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Sir—Ole Olsen and Peter Gøtzsche's full report on www.thelancet.com[1] is riddled with misrepresentation, inconsistency in the treatment of the randomised trials, and errors of method and fact, some examples of which follow.

They cite inconsistencies of reporting for the Two-County Trial. However, the individual trials and the Swedish overview inevitably differ, since the latter reclassified causes of death and redefined the study groups. This independent review of trial results is exactly the sort called for by Olsen and Gøtzsche and Richard Horton in his accompanying Commentary,[2] but was overlooked. Other alleged inconsistencies cited by Olsen and Gøtzsche are due to the numbers of deaths increasing with longer follow-up; competent meta-analysts would be aware of such change and differences between the primary studies and secondary researchers' reports.[3] The Two-County Trial is further misrepresented as two separate trials and as having failed to publish vital information. It was, in fact, one trial. We have made public more material on its design, conduct, and results than any of the other trials.

In their attempts to justify the baseline imbalance in palpable node-positive tumours in the Canadian National Breast Screening Study,[4] Olsen and Gøtzsche note that study group patients were generally treated in centres with more thorough axillary-node dissection, but did not deem this difference a source of bias. However, they wrongly cite this treatment difference as a potential source in the other trials. In the Two-County study, standard treatment according to stage of disease was applied to study and control groups.[5]

Olsen and Gøtzsche quote a significant excess of excluded previous cancers in the people aged 60–69 years in the study group of the Kopparberg part of the Two-County Trial, but do not seem to have adjusted their significance test for the multiple testing that they must have done to search for such chance heterogeneities.

The above do not inspire confidence in Olsen and Gøtzsche's judgment of study quality or for the notion that all-cause mortality is an appropriate endpoint. As if deaths from road-traffic accidents or hip fractures were in some way indicative of the effect of breast-cancer screening. We believe that Olsen and Gøtzsche referring readers to a website for details of why they were right all along, is a clever and convenient way of subverting the peer review process and shielding their work from proper scientific scrutiny. The full report is not the official Cochrane review, despite its misleading title. Olsen and Gotzsche's review is of poor quality, and, therefore, unreliable. Given this poor quality, Horton's uncritical commentary is at best ill considered. Nothing in the report or commentary disproves the finding of millions of person-years of experimental research, and dozens of previous expert reviews, that mammographic screening significantly reduces mortality from breast cancer.

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1 Olsen O, Gøtzsche PC. Cochrane review on screening for breast cancer with mammography. http://image.thelancet.com/lancet/extra/fullreport.pdf (accessed on Nov 21, 2001).
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3 Horton R. Screening mammography—an overview revisited. *Lancet* 2001; **358:** 1284–85.
4 Miller AB, To T, Baines CJ, Wall C. The Canadian National Breast Screening Study: update on breast cancer mortality. *Monogr Natl Cancer Inst* 1997; **22:** 51–53.
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Sir—I wonder why reports such as that of Ole Olsen and Peter Gøtzsche[1] raise such a lot of angry criticism. It would be rather too pessimistic and cynical to believe that the criticism stems only from self-interest of radiologists, surgeons, managers, and so on, whose daily bread depends on the continuation of mammographic screening programmes. I think that such reports shake the very basis of intuitive logic and are, therefore, not palatable. But isn't the world frequently counterintuitive?

If we believe Olsen and Gøtzsche, failure of screening to save lives is a sad fact that we might need to accept, and a plausible explanation may make it easier. Absence of benefit from screening may actually point to a very fundamental hidden biological clue. Judah Folkman[2] has elegantly shown that tumours cannot grow beyond 200 μm without stimulating their own blood supply. Thus, many primary tumours can exist in a state of dynamic equilibrium and suppress the growth of their own secondaries by antiangiogenic paracrine secretions.[3] Removal of the primary can provoke local angiogenesis from surgical trauma and release the secondaries from this inhibition and stimulate their growth.

The paracrine secretion may be proportional to the tumour size until a critical level, when it can no longer continue to inhibit the secondary growth effectively. This critical size may be different for individual tumours and could well be higher than the clinical threshold.

There is, therefore, no meaning to the term early cancer. We must realise that by age 60 years, every one of us harbours at least one of prostate, breast, thyroid, or lung cancer in a subclinical (dormant) state, which is generally harmless.[3–5]

Effective treatment of cancer and reduction in mortality from cancer in general will be possible only if we follow a strategy based on these principles. Once a primary cancer can no longer effectively inhibit its secondaries, it could be safely removed and its antiangiogenic effect replaced and supplemented so that the secondaries remain suppressed. Removal of a primary cancer at an early stage when it is effectively suppressing its secondaries will only remove the inhibition of angiogensis that will nulify any benefit from reduction of further metastasis. This mechanism could be the elusive answer to the puzzle of the disappointments of screening. We should stop talking about early cancer and start thinking about dormant cancer and inappropriate early surgery. Perhaps the only way to cure some cancers is to learn ways to live comfortably with them.

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1 Olsen O, Gøtzsche PC. Cochrane review on screening for breast cancer with mammography. *Lancet* 2001; **358:** 1340–42.
2 Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other disease. *Nat Med* 1995; **1:** 27–31.
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5 Vaidya JS, Baum M. Low-dose spiral computed tomography for lung-cancer screening. *Lancet* 1998; **352:** 236.

Sir—We have followed with interest the debate provoked by Ole Olsen and Peter Gøtzsche's work[1] on the usefulness of breast-screening programmes. Clearly, one of the most potent issues raised by their findings is what patients should be told about breast screening.

In an era of emphasis on partnership with patients and informed consent, underscored by the Kennedy principles,[2] we would expect that the current

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uncertainty about the risks and benefits of participation would be fully explained to women.

The UK National Breast Screening Programme has issued a new version of the leaflet given to women invited for screening. Entitled *Breast screening: the facts*, the leaflet, according to the National Health Service Cancer Screening Programme website,[3] purports to ensure that women are told what screening can and cannot achieve so that they can "make a genuinely informed choice about why they are attending for screening".

Social science teaches us that multiple readings are available for any text, and it is perhaps possible that one reading of this leaflet would indeed fully inform a decision about taking part in screening. Our interpretation, however, is as follows. The leaflet introduces what breast screening is with no hint of the disadvantages. It treats women's need for screening as self-evident. It draws on a persuasive discourse of "catch it early" without providing a full account of the possible risks of attempting early detection.

The leaflet suggests that the breast-screening programme has not been extended to women younger than 50 years because "it has not been proven to reduce the number of deaths from breast cancer", but makes no mention of the controversy about whether screening reduces deaths even in the ages currently screened.

The leaflet does not describe the psychological distress associated with false-positive tests, or the consequences of findings such as ductal carcinoma in situ, for which the best treatment is still unknown. The leaflet states that "Around half the cancers that are found at screening are still small enough to be removed from the breast. This means that the whole breast does not have to be removed"; it does not say that in clinically detected cancers, the breast conservation rate is even higher, at about 75%. In fact, one of the findings of Olsen and Gøtzsche's review is a paradoxical increase in mastectomy rates for screen-detected disease. No explanation is made of the possible consequences for personal insurance, including insurance of participants' children.[4] Finally, the leaflet gives no indication of the overall chance of benefit.

We suggest that this view of the benefits of breast screening is partial and potentially misleading, and that it represents a prioritising of political and professional agendas over those of patients.[5] We believe it is time we had more honest and responsible partnerships with patients supported by resources that truly reflect current evidence.

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1 Olsen O, Gøtzsche P. Cochrane review on screening for breast cancer with mammography *Lancet* 2001; **358:** 1340–42.
2 The inquiry into the management of care of children receiving complex heart surgery at the Bristol Royal Infirmary. www.bristol-inquiry.org.uk (accessed Nov 21, 2001)
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4 Thornton H. Consequences of breast screening. *Lancet.* 2000; **356:** 1033.
5 Dixon-Woods M. Writing wrongs? An analysis of published discourses about the use of patient information leaflets. *Soc Sci Med* 2001; **52:** 1417–32.

Sir—Ole Olson and Peter Gøtzsche[1] confirm their previous conclusions that there is no reliable evidence that screening for breast cancer reduces mortality.[2] Undoubtedly, this paper will raise much more heated debate.

A few months ago, we tried to find out the effect of their first publication on clinical practice. We sent a questionnaire to all Belgian gynaecologists and to a randomly selected sample of gynaecologists in four other countries (in one mailing with prepaid envelopes for responses to guarantee anonymity). We asked physicians about their screening attitudes and about whether they had modified their attitudes since the publication of Olsen and Gøtzsche's report.

In some countries (UK, Denmark, and Sweden) gynaecologists are not responsible for calling patients for mammography screening. The survey results are presented in the table. The proportion of physicians who recommend systematic screening to women was very high except in Denmark. Moreover, more than 90% of the physicians who answered the survey had not changed their attitude, whether or not they had read or heard about Olsen and Gøtzsche's first publication.

Do our results mean that physicians don't care about their patients? We don't think so. We purport that, unless harm from screening, in terms of mortality is proven, physicians may prefer to screen their individual patients, even in the absence of proof of reduced mortality.

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1 Olsen O, Gøtzsche PC. Cochrane review on screening for breast cancer with mammography *Lancet* 2001; **358:** 1340–42.
2 Gøtzsche PC, Olsen O. Is screening for breast cancer with mammography justifiable? *Lancet* 2000; **355:** 129–33.

Author's reply

Sir—Breast-cancer mortality is unreliable and biased in favour of screening. Masked endpoint committees are not the solution to this issue. First, they cannot include cardiac deaths due to radiotherapy. Second, to work in an unbiased way, death certificates and other important documents must have been completed and patients and documents selected for review without awareness of status, and it should not be possible to break the masking during any of these processes, including review of causes of death. These three assumptions seem close to impossible to fulfil. The decrease in breast-cancer mortality with screening in the Two-County study when the endpoint committee did not know status was similar to that when cause of death was assessed openly (and where we found bias in the classification process). Therefore, our findings that masked endpoint committees make biased assessments are supported.

Anthony Miller is not correct that a deliberate attempt was made in the New York study to select for masked review an equal number of cases and controls; they were selected according to prespecified criteria. Miller writes that the major difficulty was to assess cause of death when the patients had another cancer in addition to breast cancer. We noted that all-cancer mortality was similar in the groups invited to screening and in the control groups in the trials we reviewed (relative risk 1·02 [95% CI 0·95–1·10] for the two best trials and 1·00 [0·91–1·10] for the Two-County trial). If screening reduced breast cancer

	Denmark (n=264)	Sweden (n=383)	UK (n=500)	France (n=593)	Belgium (n=1150)
Response rate (%)	31	36	18	51	44
Proportion physicians recommending mammography	37	95	87	98	95
Proportion physicians not changed screening attitude (%)	90	98	93	99	98

Rate of recommendation of mammography screening after age 50 years and change in attitude to screening after reading Olsen and Gøtzsche's report

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mortality by 30%, as the Swedish trialists have claimed, relative risk for all-cancer mortality should be only 0·95 (assuming that breast-cancer mortality constitutes 18% of all-cancer mortality in women older than 40 years, as in Denmark).

Jae Hong Lee and Diana Zuckerman claim that overly aggressive treatment is a condemnation of treatment practices, not of screening. Overtreatment cannot be avoided, however. In the UK, for example, 29% of the women who had carcinoma in situ were treated by mastectomy compared with 28% of those with invasive cancer in 1999–2000.[1] The surgeons were blamed for not having treated even more women with carcinoma in situ by mastectomy. Thus, increased quality assurance would only increase this harm (carcinoma in situ is a frequent diagnosis among screened women that is rarely detected without screening, but it develops into invasive cancer in only a minority of cases).

Stephen Duffy and others had the chance of answering the crucial questions we raised in our review, such as whether the Kopparberg study was randomised, and if so, how. They did not. Laszlo Tabar tries to blame his co-workers for the inconsistencies we identified, but he has been a researcher on several of the inconsistent papers, for example those that reported fewer deaths from breast cancer with increasing follow-up than those identified initially by the masked endpoint committee. We have also noted that Tabar's main report[2] is inconsistent with the trial protocol and a later thesis. This finding reinforces our conclusion that the published data are of poor quality and very probably flawed. Contrary to their assertion, the data we present on *The Lancet* website have been extensively peer reviewed.

Miller and Stephen Senn argue that we have treated the New York and Edinburgh studies unfairly. We disagree, and note how these studies are classified is not important for our results: there is no evidence that screening decreases mortality. Contrary to what Senn asserts, our previous criticisms of the cluster randomised trials is not relevant for this finding. We furthermore doubt that retrospective exclusion of women after 18 years of follow-up, as in the New York study, is reliable.

In the absence of good arguments, some commentators try to persuade by big numbers—hundreds of thousands of patients, millions of person-years, and dozens of previous expert reviews. By contrast, Richard Horton notes in his Commentary that our results require careful reflection and discussion. We look forward to this discussion. And as long as we have not been proved wrong, our conclusions stand: there is no evidence of benefit, but evidence of harm.

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1 NHS cancer screening programmes. www.cancerscreening.nhs.uk/breastscreen/publications.html (accessed Dec 12, 2001).
2 Tabar L, Fagerberg CJ, Gad A, et al. Reduction in mortality from breast cancer after mass screening with mammography: randomised trial from the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare. *Lancet* 1985; **1:** 829–32.

Human parvovirus B19 and meningoencephalitis

Sir—Faraj Barah and colleagues (Sept 1, p 729)[1] describe the association of human parvovirus B19 infection with acute meningo-encephalitis. We have reported a patient with transient encephalopathy and hepatitis associated with B19 infection.[2]

B19 DNA was detected in the patient's serum and cerebrospinal fluid by PCR. B19 IgM and IgG were positive for the serum sample but negative for the cerebrospinal fluid. We investigated further the presence of B19 DNA in 744 stored cerebrospinal fluid samples by PCR to clarify retrospectively the contribution of B19 to central nervous system involvement.[3] Three (0·4%) samples were positive, two being samples from children with encephalopathy. The remaining one was from a patient with malignant disease who had no central nervous system involvement. B19 IgM and IgG were detected in the serum samples for these patients, but not in the cerebrospinal fluid.

A new genome type of B19 obtained from two patients with encephalopathy has been reported.[4] It was named group V as an addition to the original classification from group I to IV defined by Mori and colleagues.[5] The genome type of B19 from our patient with encephalopathy[2] was similar to group I. It seems unlikely that the limited genome type of B19 can cause encephalopathy. The pathological mechanism of encephalopathy associated with B19 infection warrants further investigation.

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1 Barah F, Vallely PJ, Chiswick ML, Cleator GM, Kerr JR. Association of human parvovirus B19 infection with acute meningoencephalitis. *Lancet* 2001; **358:** 729–30.
2 Yoto Y, Kudoh T, Asanuma H, et al. Transient disturbance of consciousness and hepatic dysfunction associated with human parvovirus B19 infection. *Lancet* 1994; **344:** 624–25.
3 Haseyama K, Kudoh T, Yoto Y, Suzuki N, Chiba S. Detection of human parvovirus B19 DNA in cerebrospinal fluid. *Pediatr Infect Dis J* 1997; **16:** 324–26.
4 Umene K, Nunoue T. A new genome type of human parvovirus B19 present in sera of patients with encephalopathy. *J Gen Virol* 1995; **76:** 2645–51.
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Macrolide treatment after coronary stent placement

Sir—In their study of treatment of infections in patients after coronary stent placement, Franz-Josef Neumann and colleagues (June 30, p 2085)[1] note in patients with high *Chlamydia pneumoniae* IgG titres a preventive effect of 4 weeks' roxithromycin treatment against restenosis (>70% lumen narrowing) and reintervention after 1 year.

They report a titre-dependent gradient for the magnitude of this treatment effect, with the greatest being in patients with the highest titres (1/512). However, these 46 individuals represent only 5% of each treatment group, which may weaken the investigators' conclusion.

In addition, Neumann and colleagues do not dissect the potential mechanisms underlying the treatment effect. The preventive effect could be the result of the specific pharmacotherapy of a subclinical *C pneumoniae* infection at the vascular site. Alternatively, the macrolide antibiotic might modulate non-specific inflammation that causes neointimal proliferation. In particular, roxithromycin also acts as an immune modulatory substance by preventing the production of proinflammatory agents such as tumour necrosis factor α, interleukin-1β, and interleukin 6.[2]

Despite *C pneumoniae* infection being a potential stimulus for a vascular inflammatory process, the assessment of IgG titres of *C pneumoniae* alone, as presented by Neumann and colleagues, does not give sufficient information about the situation at a coronary lesion for cause, extent, and nature of the inflammatory reaction. In fact, detection of *C pneumoniae* antigen and DNA in coronary lesions is more

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frequent in patients with low rather than high titres,[3] which suggests that IgG titres of *C pneumoniae* do not reflect the degree of infiltration by *C pneumoniae* in vascular lesions. Neither is it likely that titres predict the degree of local vascular or systemic inflammation. Of course, for this large trial the assessment of *C pneumoniae* antigen in the treated primary lesion as a marker of the specific infection cannot be demanded.

Alternatively, more detail about the systemic inflammatory activity would have been useful. In patients with acute coronary syndromes, immune response is activated at the site of the plaque that is reflected by activated macrophages, T lymphocytes, and mast cells, as well as systemically raised inflammatory markers such as C-reactive protein[4] or interleukin 6. In unstable and stable patients, these markers have also been associated with chronic inflammation that may trigger subsequent cardiac events.[5] Thus, measurement of such markers in the large sample of patients studied by Neumann and colleagues would have shown whether high *C pneumoniae* titres are correlated with increased inflammatory activity and to interpret the role of a possible interaction between non-specific inflammation and *C pneumoniae*-related inflammation in the process of restenosis.

Although roxithromycin seemed to reduce restenosis after coronary stenting, the possible link between *C pneumoniae* infection, systemic inflammation, and local plaque immune response remains obscure. We agree with Neumann and colleagues that the results of larger studies are to be awaited before introducing macrolide therapy in selected patients undergoing coronary intervention.

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Authors' reply

Sir—Michael Arzt and colleagues are stunned at our finding of a treatment effect of roxithromycin on restenosis. They argue that antibody titres were poor indicators of vascular infection. Indeed, the small series that correlated antibody titres with vascular *C pneumoniae* infection never showed a significant association.

Irrespective of plasma antibody titres, *C pneumoniae* antigen is prevalent in coronary atheromatous plaques (79%).[1] When we designed the study, we were aware of this notion and, therefore, did not choose seropositivity as an entry criterion. On the other hand, we found an interaction between IgG titre to *C pneumoniae* and treatment effect of roxithromycin on restenosis. We were trying to make the point that this finding suggests that it is not the infection as such but the variable host response to infection that affects restenosis and, thus, the effect of antibiotic treatment.

Arzt and colleagues propose an alternative explanation that is the non-specific effect of roxithromycin on systematic inflammatory responses of which *C pneumoniae* titres may be a reflection. To test this hypothesis they suggest analysis of C-reactive protein and interleukin 6. We agree that this issue is important and, therefore, have already analysed C-reactive protein, interleukins 6 and 10, and soluble intercellular adhesion molecule 1 in the entire cohort of patients. These analyses, which will be presented at the upcoming annual meeting of the American Heart Association,[2] unequivocally show that the interaction between *C pneumoniae* titres and treatment effect of roxithromycin has to be attributed specifically to *C pneumoniae* infection and not to non-specific inflammatory responses.

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Turner's syndrome

Sir—Advances in the understanding of Turner's syndrome have enabled a progression from the simple description of a phenotype to the correlation of genotypic variations with embryogenesis and consequent features of that phenotype. Michael Ranke and Paul Saenger (July 28, p 309)[1] cover most features of the phenotype, but neglect updates in ocular abnormalities and underlying genotypes and embryogenesis.

Ocular abnormalities are common in this syndrome, but are underestimated and often neglected. In case series of patients with Turner's syndrome, workers note amblyopia (42%), strabismus (33–38%), ptosis (16–29%), hypertelorism (10%), epicanthus (10–46%), hypermetropia (42%), and red-green colour deficiency (10%).[2–3] Additional features noted in case reports include keratoconus, glaucoma, anterior lenticonus, cataracts, and retinal neovascularisation. Unfortunately, the case series are small (24–30 patients) and most reports do not provide karyotypic information.

By contrast, Lloyd and colleagues[4] did a careful ophthalmic and chromosomal examination of four girls with mosaic Turner's syndrome. They noted anterior-segment abnormalities, including glaucoma and abnormal irides (Rieger malformation). Although mosaicism was seen in all four girls, the cell-line type varied—ie, 45,X with 46,X,idic(Y) in two cases, with 46,X,r(X) in another, and with 47,XXX in the fourth. Given this variation in karyotype, Ranke and Saenger speculate as to whether it is the direct effect of mosaicism per se on the embryogenesis of the anterior segment that causes these abnormalities.

Concern has also been voiced over possible iatrogenic eye disease in patients with Turner's syndrome. Koller and colleagues[5] reported two non-diabetic patients with Turner's syndrome who developed retinal changes mimicking diabetic retinopathy when treated with growth hormone. Ranke and Saeger note previous hypotheses suggesting a role for growth hormone in the pathogenesis of diabetic retinopathy. However neovascular changes can be seen in Turner's syndrome in the absence of exogenous growth hormone. The increased prevalence of type II diabetes mellitus (with its ophthalmic sequelae) in patients with Turner's syndrome also requires care for exogenous growth hormone and monitoring of glycaemic tolerance.

An increased awareness of the

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ophthalmic features of Turner's syndrome should enable earlier detection and treatment of sight-threatening conditions. More accurate correlation of genotype with phenotype in Turner's syndrome is now beginning to contribute to our understanding of the development and diseases of the normal karyotype eye.

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Polychemotherapy for early breast cancer

Sir—B F Cole and colleagues (July 28, p 277)[1] present the results of a mammoth mathematical and statistical exercise to analyse data on 18 000 women in 47 randomised trials.

It comes as no surprise that their findings confirm what some trials and major overviews[2,3] have already shown—systemic chemotherapy or hormonal therapy improves survival in early breast cancer. Sadly, by measuring benefit in some form of months gained, whether in overall survival or time symptom-free for disease and treatment, the researchers remind us that those months are very few, except for women with the worst of prognostic features, even for early breast cancer.

Unfortunately, to use the model, Cole and colleagues admit they have assumed 6 months of toxic effects, although regimens varied from 4 months to 36 months in the 47 trials. Their assumption that toxic effects are experienced only during chemotherapy ignores the continuation beyond the duration of chemotherapy. Thus, polyarthralgia, weight gain, resolving epilation, and lethargy are ignored. They do accept that they do not take into account the commonly severe effects of ovarian ablation by chemotherapy.

Cole and colleagues present data on their quality-adjusted time without symptoms, but, in the absence of specific patient-related data on quality of life trade-offs (and wisely refusing to extrapolate to 18 000 women undergoing at least 47 different drug regimens from their minuscule database on quality of life on 104 women taking one regimen), they allow the reader to assess benefit over the whole range of possible utility weights. Perhaps they should also repeat their analysis for the wide range of duration of toxic effects, which for many women exceeds 6 months, whereas for some it can be less.

If we are to accept these mathematical models—for that is what this exercise remains—and use them to assist us in assessing when toxic and costly treatments are justified, we should not be presented with conclusions drawn from assumption and averages.

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Authors' reply

Sir—We believe the assumptions used in our assessment of the worldwide breast-cancer trials of chemotherapy were reasonable and realistic. Our key assumption, that the duration of acute chemotherapy toxic effects is 6 months, corresponds with the duration of most current chemotherapy regimens. Moreover, in at least one large study, in which the duration of acute chemotherapy toxic effects was carefully measured, researchers noted the duration was 5·8 months on average among 816 patients randomised to a 6-month or 7-month treatment.[1] Variation of the toxic-effect duration in our analysis, as Alan Rodger suggests, would add little to the usefulness of our results.

We agree that, as with all adjuvant therapies, the late effects of chemotherapy should be considered. Fortunately, data from the International Breast Cancer Study Group[2] on more than 2000 patients suggest that the effects of chemotherapy are transient and that patients' self-reported quality of life recovers promptly after cessation of chemotherapy of various durations, and returns to that of patients not so treated.

Rodger provides an insightful remark about the use of average results for care of individual patients. Use of data from patients at highest risk of local relapse who received inadequate systemic treatment[3,4] to justify postmastectomy radiation for all women with four or more positive nodes[5] provides an excellent example.

Finally, by assessment of only the benefits of chemotherapy as in the original overview, one assumes that the data can be interpreted in a way that correctly accounts for the risks of chemotherapy. This is a strong assumption and one that we avoid in our assessment. Furthermore, our analysis provides information on the estimated magnitude of chemotherapy effectiveness according to endocrine responsiveness of the disease and use of tamoxifen. As a result, we now have a realistic view of chemotherapy benefits directly in light of its risks using a metric (ie, time gained) that is highly relevant to patients who are considering undergoing this treatment.

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