

# CORRESPONDENCE

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## Methotrexate treatment and mortality in rheumatoid arthritis

Sir—Hyon K Choi and colleagues (April 6, p 1173)<sup>1</sup> examine the associations of mortality and methotrexate treatment in patients with rheumatoid arthritis. They show convincingly that methotrexate treatment seems to be associated with a reduction in especially cardiovascular mortality and speculate that this effect might be mediated through reduction of inflammatory reactions that are shared by processes leading to rheumatic activity and to cardiovascular disease. I question whether this supposition is supported by their data.

Choi and colleagues do not show whether the group of patients with rheumatoid arthritis treated with methotrexate had better inflammatory control than the patients treated with other disease-modifying drugs. An assessment of clinical and paraclinical parameters of disease activity in the two groups during the course of treatment with or without methotrexate would have been interesting.

Another central question concerns the effect of folic acid supplementation to methotrexate treatment. In patients treated with methotrexate without folic acid, plasma homocysteine has risen in several studies, whereas folic acid supplementation has reverted this increase or even lowered plasma homocysteine concentrations to less than pretreatment concentrations.<sup>2,3</sup>

Since increased plasma homocysteine concentrations are associated with increased risk of cardiovascular morbidity,<sup>4</sup> I would have liked Choi and colleagues to have given this feature more attention. They state that the mortality ratio changed little when the analysis was restricted to the 472 methotrexate users who did not receive concomitant folic acid. When all 588 methotrexate-treated patients were included, 116 must have received concomitant folic acid. Since the mortality ratio for the whole methotrexate group was 0.4 (95% CI 0.2–0.8), the smaller proportion of patients who received methotrexate plus folic acid may have had a much lower mortality than those who did not receive folic acid. Can the two groups of methotrexate-treated patients with

or without concomitant folic acid supplementation be compared?

Choi and colleagues conclude that methotrexate can provide a substantial survival benefit. I support this conclusion, but would like to draw attention to the fact that concomitant treatment with folic acid may increase this benefit.

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Sir—Hyon K Choi and colleagues' conclusions<sup>1</sup> are, unfortunately, flawed by advanced statistics. They report an unadjusted mortality hazard ratio of 0.8 (not especially relevant) which dropped to 0.4 (very relevant) after extensive modelling. Since the results are derived from an observational cohort and not from a randomised clinical trial, the arguments for the choice of the confounding variables should be carefully considered.

As Choi and colleagues recognise, analysis of treatment effects in observational studies carries the risk of bias, the most important of which is probably confounding by indication—an observed treatment effect is biased by prognostically significant differences in disease severity. Whether this issue can be solved completely by statistical techniques adjusting for differences in disease severity, is, however, questionable.

By definition, statistical adjustment for confounding by indication only protects against biases that are recognised and measured. Many immeasurable factors might not have been captured by the censoring of weights and have altered the decision to start methotrexate. Examples are patients' unwillingness or fear of toxic effects, physicians' impression of treatment adherence, anticipated benefits, general physical condition, and so on. To argue that these elusive factors will completely efface the protective effect of methotrexate goes too far, but their possible contribution complicates the interpretation of the study.

Only random assignment assures that all prognostic factors are similarly distributed among groups, and proof of a methotrexate-attributable beneficial effect for mortality should come from the pooling and systematic follow-up of several randomised clinical trials with a methotrexate treatment group, as we did for ciclosporin.<sup>2,3</sup>

There are also other pitfalls that we think limit the interpretability of Choi and colleagues' data. Not all patients were included at the very beginning of the disease. Furthermore, from 1981, for at least 10 years, methotrexate was not a first-choice drug and most patients used it only after treatment failure with other drugs. If mortality in rheumatoid arthritis is increased, as convincingly claimed by Wolfe and colleagues,<sup>4</sup> the methotrexate group in Choi and colleagues' study might consist of patients with a favourable prognostic profile, simply because patients with the worst prognosis may have died before methotrexate was required. Therefore, mortality in the methotrexate group would be falsely deflated and inflated in the never users.

Choi and colleagues claim increased hazard ratios for starting methotrexate compared with not currently starting methotrexate for several variables related to disease severity. They argue that patients who start methotrexate have worse instead of better prognosis. Most of the severity-related variables discussed, however, represent disease activity. Variables not related to

disease activity, such as income, marital status, and comorbidity, but associated with mortality, seem to be equally distributed among groups.

The most important reason to start or change disease-modifying antirheumatic drugs (DMARDs) is generally increased disease activity. We postulate that running Cox's models with time to start any DMARD as the dependent variable would give similar results. Therefore, increased disease activity at some time point does not necessarily indicate a worse prognosis, since all patients experience periods of increased disease activity during the course of their disease.

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Sir—The low methotrexate-related mortality hazard ratios (cardiovascular and all-cause) in Hyon K Choi and colleagues' study<sup>1</sup> confirm the common view that the drug should be a first-choice DMARD. Mortality risk is not increased even in combination therapy with other DMARDs.

The inclusion of statins in a drug-risk analysis with the main emphasis on cardiovascular mortality is consistent, but their impact on mortality will be predictably low if only 2–3% of patients, treated and controls, received these drugs.

However, in our view, non-steroidal anti-inflammatory drugs (NSAIDs) are an essential group in rheumatoid arthritis that are missed out of the mortality hazard assessment, although Choi and colleagues take them into account in the calculation of the hazard ratio for starting methotrexate.

Since these drugs are frequently administered with DMARDs, at least in the early phase of rheumatoid arthritis, their inclusion would have made the study results more powerful. Therefore, assessment of NSAID drug use might contribute to resolving the conflicting results of former studies

with different designs<sup>2,3</sup> on whether concomitant use of DMARDs and NSAIDs is accompanied by an increase in mortality risk because of interaction-related higher frequencies of severe adverse effects.

An intention-to-treat approach generally causes rather an underestimation of the therapeutic effect. This is true for most outcome parameters in prospective studies. However, methotrexate may cause severe adverse reactions possibly leading to death even with low-dose monotherapy.<sup>4</sup> If the number of losses to follow-up because of severe adverse effects reaches a critical number, the estimation of mortality hazard ratios might be positively biased, since each case of methotrexate withdrawal may be interpreted an avoided death. Choi and colleagues did a sensitivity analysis to deal with this difficulty. However, it would be useful to get a more complete view of the quality and quantity of losses to follow-up and which kind of sensitivity analyses (eg, worst case, best case scenario) were used.

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Sir—Hyon K Choi and colleagues' study<sup>1</sup> is very important since methotrexate is now the most common DMARD used in rheumatoid arthritis.

A major concern in rheumatoid arthritis is the mortality linked to neoplastic disorders, especially lymphoma. One of the principal questions is whether or not the risk of lymphoma is increased by long-term administration of DMARDs, notably methotrexate.

Some studies suggest the risk of lymphoma is raised in rheumatoid arthritis, particularly in individuals treated with methotrexate.<sup>2</sup> Some

lymphoproliferative disorders share characteristics with the lymphomas that occur in immunosuppressed patients.<sup>3</sup> However, the precise incidence of lymphomas in methotrexate-treated rheumatoid arthritis patients, and their impact on the current mortality in this disease, are unknown. Although Choi and colleagues report a non-cardiovascular benefit of methotrexate, it was not possible to assess the impact of this treatment on the incidence of lymphoma.

We did a prospective national study over 3 years (1996–98) to find out the characteristics and prevalence of such lymphoma in rheumatoid patients treated with methotrexate.<sup>4</sup> 25 lymphomas were noted including 18 cases of non-Hodgkin lymphoma, only three of which were associated with the presence of Epstein-Barr virus, and seven cases of Hodgkin's disease, five of which were associated with Epstein-Barr virus. Most non-Hodgkin lymphomas were diffuse large B cell lymphomas not associated with Epstein-Barr virus. In this study, the observed annual incidence of non-Hodgkin lymphoma did not significantly exceed that in the general population in France after adjustment for age and sex (standardised mortality ratio 1.07 [95% CI 0.6–1.7]). By contrast, the annual prevalence of Hodgkin's disease in rheumatoid arthritis patients treated with methotrexate was significantly higher than that in France (7.4 [3.0–15.3]),  $p < 0.001$ ).

We saw no increase in overall risk of non-Hodgkin lymphoma in rheumatoid arthritis patients receiving methotrexate compared with the general population. Methotrexate, by reducing the activity of rheumatoid arthritis, might lower the risk of non-Hodgkin lymphoma, as previously proposed.<sup>5</sup> Nevertheless, in a few patients, this immunosuppressive treatment could also favour the appearance of a small subgroup of non-Hodgkin lymphoma and of Hodgkin's disease associated with Epstein-Barr virus.

Overall, the effects of methotrexate could allow a reduction in the prevalence and perhaps mortality related to lymphoproliferations, especially in very active rheumatoid arthritis. This point is particularly important, since the present strategies for treatment of the disease recommend early and sometimes combined use of immunosuppressors or use of powerful immunomodulators such as anti-tumour necrosis factor  $\alpha$  drugs. Thus, by lessening the activity of rheumatoid arthritis, methotrexate could provide a substantial decrease of cardiovascular mortality, but could also

have a beneficial effect on the occurrence of lymphoproliferations.

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Sir—Hyon K Choi and colleagues<sup>1</sup> report substantial survival benefit in patients with rheumatoid arthritis who were treated with methotrexate. It is now widely accepted that inflammatory autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis accelerate the progression of atherosclerosis in a way similar to the inflammatory autoimmune network. Autoantibodies related to antiphospholipid syndrome per se may not affect health but, like thrombosis, the earlier they arise in life the greater the potential threat.

In dealing with an autoimmune disorder, boundaries are frequently blurred<sup>2</sup> but the presence or not of an inflammatory component matters. Supposedly the so-called catastrophic antiphospholipid syndrome belongs to the antiphospholipid syndrome spectrum, although it remains to be elucidated whether occasionally mentioned inflammatory or fibrotic manifestations fit in the fault-tree of antiphospholipid syndrome or whether they are epiphenomena.

Thrombosis is not random; any predisposing lesion in the blood vessel may somehow link to inflammation. Inflammation is obviously absent when only antibodies linked to the antiphospholipid syndrome are detected. Substantial therapeutic progress has been achieved with low-dose aspirin or heparin in preventing thrombosis, but the antiphospholipid syndrome also

seems to favour the progression of atherosclerosis.<sup>3,4</sup> Whether in these patients this effect becomes relevant for cardiovascular events in the long-term antiphospholipid syndrome and whether inflammatory components are the common denominator or whether there is a role for other factors is unclear. The antiphospholipid syndrome has not long been identified as a syndrome and, despite medical progress, health care increasingly neglects elderly patients.

We suggest that to study these effects, long-term follow-up of symptomatic and asymptomatic patients is needed. Our target is to assess whether the downplaying of inflammation hinders progression of atherosclerosis attributed to antiphospholipid syndrome, but we think it may pay off in the long-term.

Most patients reported by Choi and colleagues had symptoms severe enough to take the risk of methotrexate. We suggest that use of anti-inflammatory agents might be a complementary approach, although inflammation is not initially visible in antiphospholipid syndrome. Patients might not want to risk taking methotrexate, but they might more willingly accept maintenance treatment with intravenous immunoglobulin infusions.<sup>5</sup>

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#### Authors' reply

Sir—In response to Ole Slot, we summarise the relevant results in the table.<sup>1</sup> Control of rheumatoid arthritis activity was better in methotrexate users than in non-users, which supports part of the survival benefit being mediated through improved rheumatoid arthritis activity. The mortality hazard ratio for combined methotrexate and folic acid compared with neither drug was 0.2 (95% CI 0.1–0.7), which suggests further benefit from folic-acid supplementation.

Robert Landewé and colleagues express concern about the reliance of our results on extensive modelling. We reported a significant 40% mortality reduction among methotrexate users (mortality hazard ratio 0.6 [0.4–0.8]) even with conventional statistical methods (time-dependent Cox's models) that are expected to provide attenuated estimates.

We agree that there are inherent shortcomings of causal inference from observational studies because of the potential for unmeasured confounding. However, additional variables that might be associated with starting methotrexate but not with mortality are insufficient to create confounding. Patients' willingness or fear for toxic effects may affect methotrexate use but it is questionable how they would affect mortality. Moreover, potential variations of these factors and general physical condition have likely already been captured by the variables for which we adjusted (eg, comorbidity score or drug use). We accounted for adherence to treatment with an exclusion criterion in our analysis. We would be pleased to see our results inspire a pooling of data from randomised clinical trials, as suggested, although such trials and especially their pooled analysis are not entirely immune to pitfalls.

	Mean difference* (95% CI)	
	MTX vs no DMARD	Non-MTX DMARD† vs no DMARD
<b>Disease activity measures</b>		
Health assessment questionnaire (0–3)	0.35 (0.12–0.57)	0.16 (0–0.31)
Number of tender joints (0–18)	2.2 (1.5–2.8)	1.1 (0.5–1.6)
Patient's global assessment (0–10)	0.9 (0.4–1.3)	0.3 (0–0.7)
Erythrocyte sedimentation rate (mm/h)	11 (3–18)	9 (3–4)

MTX=methotrexate. \*Estimated from weighted linear regression models adjusting for age, sex, rheumatoid factor, calendar year, duration of disease, smoking, education, health assessment questionnaire score, patient's global assessment, joint counts, erythrocyte sedimentation rate, prednisone status, and total DMARD count. †Sulfasalazine, penicillamine, hydroxychloroquine, or intramuscular gold.<sup>1</sup>

#### Mean differences in repeated measures of disease activity according to DMARD use

Contrary to what is indicated by table 1 of our report, Landewé and colleagues raise the possibility that the methotrexate users had more favourable prognostic factors than non-users. The rationale for this hypothesis may be that the drug was used less often in the 1980s than later. However, the mortality hazard ratio did not materially change after restricting our analysis to the 1990s. Furthermore, even if Landewé and colleagues' proposed scenario were true, no bias would ensue because our analysis contrasted individuals starting treatment with those who did not in disease of the same duration and severity.

The mortality hazard ratios for other conventional DMARDs in table 3 of our report were estimated by the same statistical analysis as for methotrexate, and, therefore, already incorporate Landewé's hypothesis on the starting of other such drugs.

In response to Uwe Tröger and colleagues, our final mortality hazard ratio estimates remained similar after adjustment for NSAID use. Data, including ours, strongly suggest that the safety and long-term tolerance of low-dose methotrexate is similar to or better than that for other DMARDs.<sup>2,3</sup> Thus, bias through loss to follow-up from adverse effects would not provide a more protective effect of methotrexate than would other DMARDs.

Furthermore, we appropriately adjusted for potential selection bias attributable to time-varying covariates that predict mortality and loss to follow-up. When we varied the censoring criterion from 1 to 3 years after last direct visit, the mortality hazard ratio for methotrexate ranged from 0.3 to 0.5, indicating that loss to follow-up is unlikely to explain our results.

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## Emotional problems in Palestinian children living in a war zone

Sir—In their report on emotional problems of children living in war zones, Abdel Aziz Mousa Thabet and colleagues (May 25, p 1801)<sup>1</sup> commit the error of inferring causality from a cross-sectional analysis. Their conclusion, that their findings are evidence that children's emotional responses to different kinds of exposure to political violence are acute and severe, is not justified. Similar reasoning would lead to the conclusion that low-calorie drinks cause obesity, since many obese people drink these beverages.

The association of emotional problems in Palestinian youths with living in a strife-ridden area does not show that either is the cause of the other. A plausible alternative explanation is that the educational, political, religious, and social environment in which Palestinian children are raised causes emotional problems and the continuing conflict in the region. Textbooks demonise Jews and encourage violence against them. Palestinian leaders review squads of kindergarten students adorned with mock explosive belts. Palestinians have been described, in the mainstream media, as having "grown intoxicated with the idea of power through death. They are exalting the most vicious acts of their own young".<sup>2</sup> Children who grow up knowing their parents' fondest hope is for them to become suicide or homicide bombers cannot be expected to perform normally on standard tests of emotional wellbeing.

Thabet and colleagues make the same error in interpreting the comparisons of the exposed group (ie, exposed to home demolitions) with the non-exposed group. Home demolition is not a random event in these areas—many homes were demolished because they were bomb factories or munitions depots. How many of the exposed children were living in such houses?

Is it any wonder that products of this society have emotional problems? I would argue that this sociological milieu is responsible for the emotional problems Thabet and colleagues note, and that the continuing conflict is not the cause, but the inevitable result, of a generation of people raised to hate.

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## Inhibitors of angiotensin-converting enzyme and physical function in older women

Sir—Graziano Onder and colleagues (March 16, p 926)<sup>1</sup> report that angiotensin-converting-enzyme (ACE) inhibitors may halt or slow decline in muscle strength in elderly women who have hypertension but no congestive heart failure (CHF). I have a few issues about the report to address.

The women they studied had been intermittently or continuously taking ACE inhibitors, compared with matched participants who were taking non-ACE-inhibitor antihypertensives or had never taken antihypertensive agents.

In previous work, administration of ACE inhibitors to individuals with heart failure has had a beneficial effect on skeletal muscle citrate synthase activity.<sup>2</sup> This enzyme is important in oxidative phosphorylation and decreases in activity or concentrations lead to a fall in ATP production, potentially reducing oxidative capacity and, therefore, exercise tolerance.<sup>3</sup> ACE inhibitors may, therefore, have a direct effect on skeletal muscle mitochondrial activity that accounts for the effects noted by Onder and colleagues.

In addition, the differences in patterns of physical activity of the patients in each group are not mentioned other than at baseline. One of the beneficial effects of ACE inhibition in individuals with cardiac failure is that it allows an increase in exercise tolerance by improving cardiovascular function. In heart failure there is a shift of expression of skeletal muscle myosin heavy chain away from fatigue-resistant myosin heavy chain 1 to the more easily fatigable 2a and 2b.

In studies of the effect of ACE inhibitors on expression of myosin heavy chains in people with heart failure, exercise capacity has improved and the ratio of myosin heavy chain fibre type has changed, with an increase in the slow myosin heavy chain 1 and a corresponding decrease in 2a and 2b.<sup>4</sup> This mechanism may be related to the greater activity seen in Onder and colleagues' patients treated with ACE inhibitors than in controls, or the ACE inhibitors might have

allowed for greater activity, which led to a change in MHC expression.

Onder and colleagues do not mention whether they think that the maintenance in exercise tolerance may have been by a similar mechanism; the increase in exercise tolerance may account for the increases seen in skeletal muscle fibre size in individuals taking ACE inhibitors.<sup>2</sup>

Furthermore, they do not discuss the potentially confounding effects of the other classes of antihypertensive agents used. Clearly patients taking  $\alpha$ -blockers,  $\beta$ -blockers, or calcium-channel blockers may have experienced the common side-effects of lethargy and fatigue,<sup>5</sup> which might diminish their capability for physical exercise. Again, it would be difficult to distinguish the lack of effect on performance from side-effects of their medications.

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Sir—The rationale for Graziano Onder and colleagues' study<sup>1</sup> arises from work on renin-angiotensin-aldosterone system antagonism in CHF. This syndrome, generally thought of as a haemodynamic disorder, has been recognised as a complex disorder characterised by multiple abnormalities also in the periphery—i.e. the skeletal muscles—which account at least partly for many of the symptoms present in these patients, such as dyspnoea, fatigue, and exercise intolerance.<sup>2</sup>

Improvement in exercise capacity is related to the magnitude of biochemical changes that occur in the skeletal muscles after renin-angiotensin-aldosterone system antagonism. Furthermore, this system contributes to the regulation of skeletal-muscle function in physiological disorders, in

that a low ACE activity in body tissues favours a positive energy balance during training in young healthy volunteers, therefore improving metabolic efficiency of the skeletal muscles.<sup>3</sup>

There seems to be a parallelism between functional status in CHF and in the physiological ageing process: both conditions are characterised by progressive exercise intolerance, largely attributable to qualitative and quantitative changes in the skeletal muscle. Similarly, functional capacity can be improved in CHF and in elderly patients with hypertension by ACE inhibitors. Onder and colleagues' report opens novel perspectives for the use of ACE inhibitors to prevent physical decline in elderly people without heart disease.

Although compared with other antihypertensive drugs, continuous ACE-inhibitor use led to a significantly lower decline in muscle strength and walking speed, we do not know which other drugs were used. Subgroup comparisons would be useful for  $\beta$ -blockers. Norepinephrine concentrations are raised in elderly people without heart disease<sup>4</sup> and adrenergic activation is strongly associated with cachexia in CHF, a disorder characterised by substantial loss of fat and lean tissue. Furthermore, in a COPERNICUS substudy,<sup>5</sup> carvedilol prevented and even reversed cardiac cachexia in severe CHF. Therefore, it is possible that  $\beta$ -blockers might have effects similar to those of the ACE inhibitors on functional capacity in elderly people.

Some clinicians may be reluctant to administer  $\beta$ -blockers to elderly people, but we should bear in mind that this class of drugs was once contraindicated in CHF, yet now represents one of the most powerful means to reduce mortality in this disorder.

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Sir—Graziano Onder and colleagues' did their study<sup>1</sup> on the basis that ACE inhibition improves blood flow in skeletal muscle in association with increased glucose and aminoacid uptake, and lowers cytokines that affect incidental disability and nutritional status, thereby slowing physical decline in elderly people. However, they do not comment on whether ACE inhibitors might have improved aspiration pneumonia rather than led to a decline in skeletal muscle strength. The recorded benefit may be attributable to their effects on symptomless dysphagia<sup>2</sup> rather than skeletal-muscle mechanism.

In several studies, ACE inhibitor use has been associated with a reduced incidence of pneumonia, particularly in elderly people.<sup>3,4</sup> Moreover, deletion of the allele of ACE gene is associated with the increased risk of pneumonia in elderly people.<sup>5</sup> Thus the improvement of symptomless dysphagia and reduced risk of pneumonia afforded by ACE inhibitors may play a notable part in maintaining physical performance in elderly people.

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Authors' reply

Sir—Ketan Dhatariya suggests that the beneficial effect of ACE inhibitors on physical performance we report may be mediated by positive changes in the skeletal muscle and directly related to an improvement in exercise tolerance. This hypothesis is based on studies done in individuals with CHF, which suggests

that ACE inhibitors have an impact on exercise capacity as a consequence of improvements in cardiovascular function. Despite the fact that hypertensive women included in our study had no clinical evidence of CHF, we agree that this mechanism could plausibly explain our findings. As Dhataria points out, physical performance and skeletal muscle strength are closely related,<sup>1</sup> and further studies are necessary to distinguish specific effects of ACE inhibitors on these two measures.

In addition, Dhataria states that the side-effects of  $\alpha$ -blockers,  $\beta$ -blockers, and calcium-channel blockers may have diminished patients' capability for physical activity, explaining the difference between the ACE-inhibitor and non-ACE-inhibitor groups. We do not think this effect is the case, since fatigue and lethargy can be seen even in ACE-inhibitor users.<sup>2</sup> Moreover, the fact that patients never using antihypertensive drugs during the study period had a significantly greater decline in muscle strength and walking speed than did continuous ACE-inhibitor users makes this hypothesis unlikely.

Mariantonietta Cicoira suggests that  $\beta$ -blockers might have effects similar to those of ACE inhibitors on functional capacity in older adults. This statement is based on clinical trials done in patients with CHF, but no evidence suggests that these results can be generalised to patients free from CHF.<sup>3</sup> In our sample, the use of  $\beta$ -blockers at baseline was similar among patients who had ever used ACE inhibitors and those who had never used ACE inhibitors (13 vs 16%). In addition, baseline use of  $\beta$ -blockers showed no longitudinal association with change in walking speed or muscle strength.

Finally, Kiyohisa Sekizawa states that the beneficial action of ACE inhibitors on physical performance may be attributable to their effects on pneumonia. This hypothesis, despite being intriguing, seems an unlikely explanation for our findings, since loss of physical function in old age is frequently a progressive phenomenon, not a direct consequence of acute events such as pneumonia.<sup>4</sup>

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## Central retinal vein occlusion in a patient with rheumatoid arthritis taking rofecoxib

Sir—Helen Frankish, in her April 20 news item (p 1410),<sup>1</sup> describes why some newly developed non-steroidal anti-inflammatory drugs (NSAIDs) might increase the rate of cardiovascular events in predisposed populations compared with traditional NSAIDs.

The largely used non-selective NSAIDs inhibit cyclo-oxygenase (COX)-1 and COX-2 isoenzymes and are effective in the treatment of rheumatoid arthritis. New selective COX-2 inhibitors, such as rofecoxib, preserve the therapeutic benefits of NSAIDs, although questions have been raised about potential effects on cardiovascular thrombotic events. We report a patient with ocular thrombosis treated with a selective COX-2 inhibitor.

A white woman aged 72 years who had rheumatoid arthritis was receiving 25 mg rofecoxib daily for 6 months. 3 days after the dose was doubled to 50 mg daily, she noticed a sudden painless decrease of vision in her right eye. Her visual acuity was 20/400 in the right eye and 20/20 in the left eye. On slit-lamp examination, the anterior segment was normal in both eyes. Biomicroscopy of the right eye showed dilated and tortuous retinal veins and many flecked and flame-shaped haemorrhages in the midperiphery. In addition, the central retina, including the macula, had an intraretinal oedema—typical signs of a central retinal vein occlusion. Fundus examination of the left eye remained unremarkable.

Central retinal vein occlusion is presumably a thrombosis of the central retinal vein at the lamina cribrosa, the fenestrated sclera, where arteria and veina centralis enter the globe together with the nerve fibres of the optic nerve. A narrowing of the vein may cause turbulence, endothelial damage, and

thrombus formation. Various systemic disorders, including arterial hypertension, diabetes mellitus, dyslipidaemia, and systemic vasculitis, are associated with central retinal vein occlusion and play an important part in the pathogenesis, therapeutic strategies, and prognosis of the ocular and systemic disease.<sup>2</sup>

In the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial,<sup>3</sup> patients with rheumatoid arthritis taking rofecoxib had a five-fold higher incidence of myocardial infarction than they did receiving standard NSAID therapy with naproxen. The occurrence of upper gastrointestinal bleeding was, however, significantly lower with rofecoxib.

A proposed mechanism to explain this observation is that non-selective NSAIDs have a cardioprotective effect, due to thromboxane A2 inhibition, but COX-2 inhibitors have no inhibitory effect on thromboxane and lower the beneficial vascular effects of prostacyclin. This imbalance of thromboxane and prostacyclin potentially interferes with homeostatic functions and may accelerate the risks of spontaneous thrombotic events in predisposed patients.<sup>4</sup> Patients with rheumatoid arthritis commonly have raised von Willebrand factor, tissue plasminogen activator, fibrinogen, or plasma viscosity, and may be more prone to respond to thrombotic stimuli.

The precise role of COX-2 cannot be elucidated by this evidence-based report. On the basis of the limited experience to date, selective COX-2 inhibitors do not accelerate atherogenesis, although they may induce prothrombotic effects under certain conditions. In most patients, COX-2 inhibitors are safe, given the small number of thrombotic events. Few patients with predisposed thrombosis may be at risk for cardiovascular and ocular thrombotic events.

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## Burnt-out DCIS of the breast: worth a second look?

Sir—Local regression, or so-called healing, of ductal carcinoma in situ (DCIS) of the breast was described almost 70 years ago.<sup>1,2</sup> There has been little interest in the phenomenon since. Our interest has arisen since the routine use of core biopsy for the diagnosis of mammographically detected calcifications. We recognise foci of burnt-out DCIS increasingly commonly, and believe this finding has some implications for current practice. The entity has probably been under-recognised in the past, and a more detailed study of the process might be worthwhile.

Local regression is characterised by progressive (comedo) necrosis in an area of high nuclear grade DCIS, leading to complete loss of epithelium and a granulomatous or histiocytic reaction to the necrotic ductal contents, generally associated with fibrosis and chronic inflammation in ductal and periductal tissue. The endpoint may be a calcific mass surrounded by fibrosis, or calcific material within a duct without epithelium, or even a small sclerosed duct structure without calcification. In most cases we have seen with these appearances, further levels of section or excision biopsy have shown foci of viable high-grade DCIS.

From our experience of the phenomenon in core biopsies over the past 6 years, we suggest that in core biopsy samples of mammographically detected microcalcification lesions, the finding of large calcifications in ducts or a granulomatous or histiocytic reaction, without an epithelial lining, may represent burnt-out DCIS. Such findings cannot be dismissed as benign. Further follow-up is necessary, possibly even excision biopsy. These appearances have in the past been accepted by some as representing calcified duct ectasia or periductal mastitis in peripheral breast tissue. The exact mechanism is uncertain. A tissue reaction to necrotic material is probably part of the process. There may be an element of ischaemia relating to ductal fibrosis and chronic inflammation, and an immune-mediated component cannot be entirely discounted. Whether high-grade DCIS can completely regress or whether this is always a focal phenomenon is uncertain.

Tissue studies might include an examination of the frequency of this appearance in routine screening

situations, the extent of the process in surgically excised high-grade DCIS, and an assessment of the vascular and lymphoid component of periductal tissue in these cases. To find out whether there was a negative association with invasive carcinoma would be useful. Study of the previous radiological appearances and subsequent follow-up in such cases might also be important.

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## Guidelines for treatment of upper gastrointestinal cancer

Sir—Clinicians involved in the care of patients with upper-gastrointestinal cancers have expressed reservations concerning the evidence for and implementation of the UK Department of Health Guidance on Commissioning Cancer Services (GoCC) document on these disorders.<sup>1</sup> The document advises that all treatment—curative and palliative—for oesophagogastric and pancreatic cancers should be undertaken in hospitals serving minimum populations of 1–2 million. All other hospitals should be limited to diagnosis.

The GoCC document reports a volume-to-outcome effect for oesophagogastric and pancreatic cancer, principally based on a 1996/97 study from southwest England of 571 patients undergoing oesophageal or gastric resection. Despite its referenced date of 1999, this audit was not available to the wider scientific community until July, 2002. Other data quoted in the GoCC evidence relates to the USA, where the geography and system of health provision differ entirely from the UK, use a cut-off of five operations per year to distinguish between high-volume and low-volume operators, and are taken from the 1980s.

Neither in a Scottish study<sup>2</sup> of 3290 patients, nor in a West Midlands study<sup>3</sup> of 1125 patients undergoing oeso-

phageal resections, were volume-to-outcome effects noted. In Scotland, centralisation of oesophageal cancer surgery resulted in a non-significant reduction in perioperative mortality, but with no change in survival at 1 year and 3 years, and an increase in the time between diagnosis and treatment. A report from Holland does show a volume-outcome relation for oesophageal cancer surgery, but highlights the disadvantages of centralisation in provision of treatment of emergency cases that cannot be transferred, and the diminished ability of disenfranchised hospitals to recruit staff of sufficient calibre.<sup>4</sup>

Cancer networks are being instructed to enforce service provision based on minimum populations of 1 million without reference to the audited outcome data of surgical units. Removal of upper-gastrointestinal-cancer surgery, including palliative procedures such as bypass surgery, and oesophageal and biliary stenting, will result in the rapid deskilling in all levels of medical, theatre, and ward staff, such that the management will inevitably worsen for patients with benign upper-gastrointestinal diseases. The president of the British Society of Gastroenterology has questioned the basis and implications of these guidelines.<sup>5</sup>

It is inappropriate to enforce such changes at a time when the UK has an inadequate number of sufficiently experienced surgeons and physicians, when the training and experience of newly appointed consultants is subject to debate, especially when the evidence for such changes is flimsy.

We all wish to ensure improved care for patients with upper-gastrointestinal cancers. We urge the Department of Health to reassess the evidence and recommendations on minimum populations. Common sense needs to be applied before the experience of consultants and nursing staff of all disciplines is lost forever to the harm of patients with upper-gastrointestinal disorders, and the provision of acute services.

TCBD and 71 consultant surgeons, gastroenterologists, oncologists, intensivists, and radiologists from 21 UK hospitals were signatories on this letter.

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## Protein energy malnutrition and risk of tuberculosis infection

Sir—In your June 15 Editorial,<sup>1</sup> you discuss the UN World Food Summit. In June, 2002, the UN Food and Agriculture Organization (FAO) and the World Food Programme (WFP) warned at the World Food Summit of a severe, mainly drought-induced, food crisis affecting about 13 million people in six southern African countries—Lesotho, Malawi, Mozambique, Swaziland, Zambia, and Zimbabwe—which are also struck by highly prevalent HIV-1 infection (around 15–36% in adults)<sup>2</sup> and tuberculosis (co-infection in a third of HIV-1-infected people). We stress the potential impact of protein energy malnutrition on the incidence of tuberculosis.

There is strong evidence that primary malnutrition raises the incidence and exacerbates clinical manifestations of tuberculosis.<sup>3</sup> In a World War II study, Leyton<sup>4</sup> studied hard-working prisoners of war in a German camp. Soviet prisoners had a daily caloric intake of about 1350 kcal, whereas UK prisoners received additional Red-Cross food supplies, which doubled their daily caloric intake. The rate of radiologically and microscopically confirmed pulmonary tuberculosis was 15.8-fold higher in the Soviet prisoners than in the UK prisoners (19.0 vs 1.2%). Leyton concluded that the lack of food, not poor natural immunity, was the main cause of this difference in rate.

Experimental data have since corroborated this observation. Mice with protein calorie malnutrition infected intravenously with *Mycobacterium tuberculosis* expressed less interferon-gamma, tumour necrosis factor  $\alpha$ , and inducible nitric oxide in their lungs than did control mice. Malnourished mice also had decreased granulomatous reaction,

higher lung bacillary load, and a more fatal tuberculosis course than did well nourished mice, which could be reversed by restoring a diet with normal protein content.<sup>5</sup> In other studies, protein malnutrition has impaired T-cell function, particularly the production of T-helper-1 cytokines and macrophage antimycobacterial effector functions.

The relation between malnutrition and tuberculosis should be highlighted in the context of the highly prevalent southern African HIV-1 and tuberculosis co-infection. HIV-1 infection devastates CD4 lymphocyte numbers but has similar immunological consequences to malnutrition, by suppressing T-helper-1 and macrophage functions, which may have an additive effect in raising tuberculosis incidence, morbidity, and mortality. Malnutrition will also increase the incidence of tuberculosis in HIV-1-negative individuals. Finally, HIV-1 infection and tuberculosis impair the nutritional state, which can lead to slim disease and consumption, respectively.

Thus, a merciless vicious circle exists between these two major infections and nutritional deficiency. Therefore, an effective approach to control HIV-1 and tuberculosis infection in sub-Saharan Africa, and particularly southern Africa, needs to include food security. World leaders at the G8 summit in July, 2000, decided to tackle the three priority diseases of poverty—HIV-1 infection, tuberculosis, and malaria—and to reduce prevalence of and death from tuberculosis by 50% by 2010. The way to achieve this ambitious task is paved by medical difficulties and by societal issues, including provision of an adequate food supply.

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## Drug development for neglected diseases

Sir—Patrice Trouiller and colleagues (June 22, p 2188)<sup>1</sup> issue a clear call to do more for globally neglected diseases. The Global Forum for Health Research was established to help correct the 10/90 gap—ie, the fact that less than 10% of funds spent annually by the public and private sectors combined goes on 90% of the world's health problems.

The Global Forum encourages the application of priority-setting methods to identify research priorities, promotes a discussion of these priorities by various constituencies, including governments, donors, the private sector, civil society, and the media, and fosters the establishment of networks in research priority areas to help correct the 10/90 gap.<sup>2</sup>

The Global Forum and partners reported global investments in health research of US\$73 billion in 1998 from private and public sources,<sup>3</sup> and are currently updating this amount. Understanding and documenting the 10/90 gap is the first step towards correcting it.

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## DEPARTMENT OF ERROR

*Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial*—In this Article by A G G Turpie and colleagues (May 18, p 1721), in table 1, the number of patients in the column headed Efficacy analysis—Fondaparinux once daily should be “n=787” and the number of patients in the column headed Efficacy analysis—Enoxaparin twice daily should be “n=797”.

*Sexual mixing patterns and sex-differentials in teenage exposure to HIV infection in rural Zimbabwe*—In this article by Simon Gregson and colleagues (June 1, p 1896), in figure 3 the open bars should represent 17–20 years and the shaded bars 21–24 years.

*Association between conformational mutations in neuroserpin and onset and severity of dementia*—In this Mechanisms of disease article by Richard L Davis and colleagues (June 29, p 2242), there was an error in figure 1, panel B. The lower of the two residues denoted “S49” should have been “S52”.