

to end up paying more in debt servicing than before they received their debt relief. This is because such countries are currently repaying debt to the World Bank and International Monetary Fund while repayments to creditor nations under bilateral agreements are not being honoured. When the World Bank and International Monetary Fund debts are cancelled under the initiative, this will release cash reserves and oblige those countries to start repaying creditor countries. And, as if proving the cynics right, Uganda's benefit has been short lived: a fall in coffee prices has rendered Uganda's debt unsustainable again—only 10 months after it received assistance under the heavily indebted poor countries initiative.<sup>10</sup>

Earlier this year Jubilee 2000's campaign cajoled a positive response from the governments of Britain, Canada, Germany, and the United States, as well as encouraging noises from the World Bank and International Monetary Fund. But recent reports indicate that the world's poor are likely to be disappointed when the G8 countries meet in Cologne next week.<sup>11</sup> The International Monetary Fund is leading the campaign to draw back from the extent of debt relief that some of the G8 countries had been promising. It is offering a three year wait for debt relief rather than six, but countries still have to maintain structural adjustments for six years, with reapplication of the debt if they fail.

Cancelling debt for the world's poorest people is a fitting way to welcome the new millennium. The world's richest finance ministers should seize the

opportunity when they meet next week. The rest of us should join the many worldwide events that Jubilee 2000 is holding between now and the G8 meeting in Cologne—for example, on 13 June supporters of debt cancellation will be linking arms across the River Thames in London. As the playwright Harold Pinter put it: "It's actually a state of war. The powerful against the rest."<sup>12</sup> Let's end the war and set the slaves free.

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## Nutritional hyperhomocysteinaemia

### *Evidence mounts for its role in vascular disease*

**A** raised concentration of serum homocysteine is increasingly being implicated as a risk factor for clinical vascular disease. It is known to be injurious to the vascular endothelium in animals,<sup>1</sup> and many reports have now confirmed the presence of raised homocysteine concentrations in patients with peripheral vascular disease, myocardial infarction, stroke, and venous thromboembolism. Indeed, moderate and intermediate increases in homocysteine concentration have been found in up to 40% of patients with vascular disease<sup>2</sup> and in up to 35% of patients with venous thromboembolism.<sup>3</sup> The obvious question is: is this cause or effect? And, if it is causal, should we be screening for and treating hyperhomocysteinaemia?

All circulating homocysteine is derived from methionine in the diet, and it is removed by either remethylation to methionine or conversion to cysteine via a transsulphuration pathway. Classic homocystinuria, a rare autosomal recessive condition, of which premature vascular disease and thrombosis are major features, is the result of a deficiency of the enzyme for transsulphuration, cystathione  $\beta$ -synthetase. The heterozygous state for cystathione  $\beta$ -synthetase deficiency occurs in 1 in 70 to 1 in 200 of the general population<sup>4</sup> and is associated with moderate increases in serum

homocysteine. More common, but less severe, genetic changes in enzymes implicated in the remethylation pathway (methylene tetrahydrofolate reductase and methionine synthetase) may also be responsible for milder increases in homocysteine concentrations (above 15  $\mu\text{mol/l}$ ). Genetic mutation of methylene tetrahydrofolate reductase shows geographical variations. A thermolabile variant of methylene tetrahydrofolate reductase is extremely common in North America, with an overall allele frequency of 38% in the general population.<sup>5</sup> Nevertheless, it is thought to result in hyperhomocysteinaemia only in the presence of folate deficiency.<sup>5</sup>

Early reports focused on premature vascular disease in young patients without classical risk factors. A high proportion of these patients have cystathione  $\beta$ -synthetase deficiency and other enzyme abnormalities. Genetic abnormalities, however, cannot account for the frequency of raised blood homocysteine concentrations (hyperhomocysteinaemia) seen in the wider population of patients with vascular disease, and attention is now being focused on diet induced hyperhomocysteinaemia as a cause of increased vascular risk, probably acting synergistically with more conventional risk factors.<sup>6</sup> Essential cofactors for the enzymes of homocysteine metabolism (vitamin B-6, vitamin

B-12, and folic acid) are acquired only from the diet. The active form of vitamin B-6 (pyridoxal phosphate) serves as the cofactor for two successive steps of the transsulfuration pathway; and the active forms of vitamin B-12 and folic acid serve as cofactor (methylcobalamin) and cosubstrate (methyltetrahydrofolate), respectively, for the enzymes in the remethylation pathway.<sup>4</sup>

Nutritional studies in patients with vascular disease and controls have shown an inverse correlation between concentrations of vitamin B-12 and folate and those of homocysteine.<sup>7</sup> Selhub et al found that 40% of the elderly population was deficient in folate,<sup>8</sup> and in patients with subnormal levels of folate 84% had raised homocysteine concentrations. The correlation between B-6 deficiency and raised homocysteine concentrations is less clear, but as the population with vascular disease is likely to have other risk factors, including smoking, it is interesting to note that smokers have a significantly lower vitamin B-6 level than non-smokers.<sup>9</sup>

Irrespective of its cause, moderate and intermediate hyperhomocysteinaemia is readily correctable by folate, betaine, or vitamin supplementation. Homocysteine concentrations in folate deficient patients can be normalised by folic acid supplementation,<sup>7</sup> which increases the availability of the cosubstrate, methyltetrahydrofolate, and drives the pathway for homocysteine remethylation. The effective dose of supplementation has not yet been determined, but maximal therapeutic effect is seen with doses over 400 mg and after four to six weeks.<sup>10</sup> Betaine serves as an alternative methyl donor to folic acid in the recycling of homocysteine to methionine. Vitamin B-12 normalises homocysteine concentrations in patients who are vitamin B-12 deficient but not in normal subjects.<sup>11</sup> Vitamin B-6 alone does not reduce plasma homocysteine concentrations,<sup>11</sup> but when it was administered in combination with folic acid homocysteine concentration was lowered by 50%.<sup>7</sup> Elderly patients taking vitamin B-6 supplements of 100-200 mg/day showed a 73% reduction in the risk of angina and myocardial infarction, with an average increase in lifespan of eight (range 7-17) years.<sup>12</sup>

Thus homocysteine seems likely to be a risk factor, interacting with other risk factors, applicable to all patients with vascular disease and not just those with premature disease. It seems logical to assume that a reduction in homocysteine concentration will reduce the risk of atherosclerotic lesions and thrombosis, but there are as yet no published data to prove this. The potential impact of treating a diet induced risk factor for atherosclerosis is enormous: such treatment is safe and inexpensive and does not inhibit lifestyle. It is time for clinical trials to determine the impact of treatment to reduce homocysteine concentrations on the subsequent course of vascular disease.

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## Clinical Evidence

*This month sees the publication of a new resource for clinicians*

This week's *BMJ* carries a sample of information from a new resource for clinicians, *Clinical Evidence*, which will be launched later this month (p 1600). The inspiration for *Clinical Evidence* came in a phone call in 1995. Tom Mann and his colleagues at the NHS Executive asked the *BMJ* to explore the possibility of developing an evidence "formulary" along the lines of the *British National Formulary*. They recognised that clinicians were under increasing pressure to keep up to date and to base their practice more firmly on evidence but that few had the necessary time or skills to do this. Their idea was to provide a pocket-size book

containing concise and regularly updated summaries of the best available evidence on clinical interventions.

A small team at the *BMJ* set to work. In partnership with the American College of Physicians we convened an international advisory board, held focus groups of clinicians, talked to patient support groups, and adopted countless good ideas from early drafts by our contributors. Throughout we kept in mind an equation set out by Shaughnessey et al.<sup>1</sup> This states that the usefulness of any source of information is equal to its relevance multiplied by its validity, divided by the work required to extract the information. To be as useful as

*Clinical review*  
p 1600

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