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.[4]

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.[7] Selhub et al found that 40% of the elderly population was deficient in folate,[8] 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.[9]

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,[7] 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.[10] 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.[11] Vitamin B-6 alone does not reduce plasma homocysteine concentrations,[11] but when it was administered in combination with folic acid homocysteine concentration was lowered by 50%.[7] 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.[12]

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.

Clinical review
p 1600

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.[1] 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

See advertisement opposite p 1598 (CR edition), p 1621 (GP), p 1567 (Compact and International)

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possible we aimed for high relevance, high validity, and low work in terms of the reader's time and effort. We also kept in mind principles of transparency and explicitness. Readers needed to understand where our information came from and how it was assembled.

The first issue of *Clinical Evidence* will contain summaries on the prevention and treatment of about 70 common conditions. Each summary is based on a thorough search and appraisal of the literature, looking for good systematic reviews and, where these are lacking, individual randomised controlled trials. The summaries are written by clinicians with skills in epidemiology and are extensively peer reviewed.

Clinical Evidence joins a growing number of sources of evidence based information for clinicians. But it has several features that, we think, make it unique.

Firstly, its contents are driven by questions rather than by the availability of research evidence. Rather than start with the evidence and summarise what is there, we have tried to identify important clinical questions and then to search for and summarise the best available evidence to answer them.

Secondly, it identifies but does not try to fill important gaps in the evidence. As Jerry Osheroff at the American College of Physicians puts it, *Clinical Evidence* presents the dark as well as the light side of the moon. We feel that it will be helpful for clinicians to know when their uncertainty stems from gaps in the evidence rather than gaps in their own knowledge.

Thirdly, it will be updated every six months. This means that clinicians can rely on it to keep them up to date in the topics that are covered.

Finally, and importantly, it specifically aims not to make recommendations. This is because we feel that simply summarising the evidence will make it more widely applicable. The experience of the clinical practice guideline movement has shown that it is nearly impossible to make recommendations that are appropriate in every situation. Differences in individual patients' baseline risks and preferences, and in the local availability of interventions, will always mean that the evidence must be individually interpreted rather than applied across the board. *Clinical Evidence* provides the raw material for developing locally applicable clinical practice guidelines and for clinicians and patients to make up their own minds on the best course of action. We supply the evidence, you make the decisions.

Our expectation is that *Clinical Evidence* will evolve rapidly in its early years, just as the *British National Formulary* did when it first appeared. Indeed, *Clinical Evidence* may well become a family of products, appearing in different formats (including electronic) and languages for different audiences. In particular, it will evolve in response to the needs of clinicians. We have tried hard to anticipate those needs (not least by involving clinicians at every stage), but it is only when people begin to use *Clinical Evidence* in daily practice that we can know how best to develop it. We hope you will let us know what you think of the sample in this week's journal, and of the first issue of *Clinical Evidence* when it appears later this month.

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Antithrombotic therapy in cancer

Low molecular weight heparins may have a direct effect on tumours

Two recent studies from Scandinavia[1 2] have reinforced the clear association between thrombosis and malignant disease that was first recognised by Trousseau in the 19th century.[3] These population based analyses of cancer risk involved about 86 000 patients with venous thromboembolism, 4200 of whom had cancer. The observed incidence of cancer (especially pancreatic and ovarian) was 1.3 times the expected incidence among the Danish patients with either deep vein thrombosis or pulmonary embolus and 3.2 times the incidence among the Swedish patients. As a corollary, patients with established cancer are at increased risk of venous thromboembolism, which is potentially fatal. Patients with cancer are nearly twice as likely to die of pulmonary embolism in hospital as those with benign disease, and about 60% of these deaths occur prematurely.[4] The hypercoagulable state of malignancy reflects tumour elaboration of tissue factor, the physiological procoagulant.[5] Might antithrombotic treatment help reduce this high risk in patients with cancer?

The risk of thrombosis is further increased when patients receive therapeutic interventions for their cancer. After an abdominal operation the risk of deep vein thrombosis is twice that in non-cancer patients, and the risk of a fatal pulmonary embolus is increased fourfold without routine thromboprophylaxis.[3] Chemotherapy also carries a serious thrombotic risk: the incidence of thrombosis was 9% in a group of postmenopausal women receiving combined chemotherapy and hormonal therapy.[6] Part of this incidence may reflect the route of administration of drugs, since the use of central venous lines in patients with cancer is associated with thrombosis rates of 30-60%.[7] More importantly, by damaging the endothelium, cytotoxic

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