Hyperhomocysteinaemia and premature coronary artery disease in the Chinese

SIR,—We were interested by the study by Lolin and colleagues.1 The Chinese patients with premature coronary artery disease had higher concentrations of folate in serum and erythrocytes, and higher serum vitamin B6 than healthy control subjects. There was no significant difference in prevalence of fasting hyperhomocysteinaemia; however, there was a significantly higher prevalence of hyperhomocysteinaemia following methionine loading in patients versus controls. There was a significant difference in fasting and post-methionine load plasma total homocysteine concentrations (4.9 ± 3.3 μmol/l) as emerged as unadjusted versus controls (P = 0.004 and P = 0.003).

Hyperhomocysteinaemia may emerge due to genetic factors, for instance from deficiency of the enzyme cystathionine β synthase (CBS), which participates in a transulfuration pathway, or from thermodabile or mutant enzyme methylene-tetrahydrofolate reductase (MTHFR) which synthesises 5-methyltetrahydrofolate, or from inborn errors of cobalamin transport and metabolism. Lower concentrations of vitamins B6, B2, and folate are rare in serum or plasma may also be associated with hyperhomocysteinaemia. Vitamins B6, B2, and folate are coenzymes for enzymes methionine synthase, CBS, and MTHFR, respectively. 5-Methyltetrahydrofolate is a methyl donor for methylation of homocysteine into methionine. Deficiency of these vitamins in blood may occur because of dietary or environmental factors.

Miller and colleagues4 have indicated that vitamin B6 deficiency in humans or rats may not be associated with fasting hyperhomocysteinaemia. Fasting plasma tHcy concentrations in vitamin B6 deficient rats were not significantly different from those in control rats; however, the folate deficient rats had plasma tHcy concentrations nearly 10-fold higher than control rats (P = 0.001). During methionine loading, vitamin B6 deficient rats exhibited a dramatic elevation of plasma tHcy concentrations which persisted for four hours or longer (P < 0.001). Folate deficient rats did not show any significant increase in plasma tHcy.1,4

My colleagues and I have shown that serum folate and vitamin B12 concentrations had significant influence on fasting plasma tHcy concentrations; however, the influence of vitamin B6 on fasting plasma tHcy was weak, probably due to smoking.4

These findings may indicate that homocysteine response during methionine loading may be different for folate or vitamin B6 deficiency. Folate deficiency may be associated with fasting hyperhomocysteinaemia. Methionine loading test may be used to uncover post-load hyperhomocysteinaemia which may be associated with deficiency of vitamin B6 or homocysteine deficiency of CBS.

Therefore, it may be interesting to measure concentrations of vitamin B6 in plasma or whole blood to investigate a potential role of vitamin B6 in the development of hyperhomocysteinaemia in these patients. This might be important because patients with premature coronary artery disease had higher concentrations of folate in serum and erythrocytes. Measurement of vitamin B6 in a serum from patients and control subjects may also add new information in the study.

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References

This letter was shown to the authors, who reply as follows:

SIR,—We thank Dr Mansoor for his helpful comments on our study, particularly on the importance of finding the causes(s) for hyperhomocysteinaemia in patients. Our suggestions about measuring B6 and B12 are very welcome. They are, however, based on the observations that the incidence of post-methionine hyperhomocysteinaemia is significantly higher in patients than in controls. The number of subjects in our study was small and, though not statistically signifi- cant, there was a difference between patients and controls regarding fasting hyperhomocysteinaemia (22% vs 4.8%, respectively). Further, the mean serum homocysteine levels were significantly higher in patients than in controls in both the fasting and post-methionine states, although the difference between the fasting levels was less striking.

Dr Mansoor pointed out the many causes for hyperhomocysteinaemia. We noted that low serum or plasma folate levels were associated predominantly with fasting hyperhomocysteinaemia, and B12 deficiency or homocysteine deficiency of cystathionine β synthase (CBS) and hyperhomocysteinaemia. Our study showed that in the Hong Kong Chinese, folate and B12 deficiencies were unlikely to be aetologically important. This may have contributed to the relatively low incidence and modest fasting, hyperhomocysteinaemia. The striking response to methionine may well have been accounted for by heterozygous deficiency of CBS. Dietary deficiencies of B6 and B12, although possible, are less likely although we will follow the suggestions of Dr Mansoor. Both vitamins are present, among others, in poultry, meat, fish, soya bean (particularly B6), asparagus (particularly B6), spinach, and broccoli, all of which are eaten in abundance in this population throughout the year. A definitive utilisation of these co-enzymes through deficiency of CBS and the presence of the heat labile or a mutant 5- methyltetrahydrofolate reductase is, however, a distinct possibility and we are presently investigating these enzymes in our population.

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Hyperhomocysteinaemia and coronary athero-sclerosis

SIR,—I read with great interest the article on hyperhomocysteinaemia and coronary artery disease in Hong Kong Chinese patients.1 As suggested by the title of the accompanying editorial,1 hyperhomocysteinaemia has emerged as an important risk factor for the development of coronary artery disease.

Homocysteine in human plasma arises solely from the breakdown of the essential amino acid methionine via dietary sources. Dietary homocysteine is complexed to various thiol, and does not appear under normal circumstances to influence plasma homocysteine.2 The plasma concentration of homocysteine is strictly controlled and kept within a very narrow range in normal subjects, either by its degradation via cystathionine to cysteine and pyruvate, or by methylation to methio- nine.3 Although it can be made to rise by ingestion of a very high so-called “loading dose” of methionine in normal subjects on normal diets, such postprandial increases are small, with plasma homocysteine concentra- tions declining rapidly to the normal range. The study by Lolin and colleagues1 suggests that in the Hong Kong Chinese patients hyperhomocysteinaemia is associated with genetically inherited abnormalities in enzymes associated with its metabolism. Thus, while patients with reduced concentrations of cystathionine β synthase, or 5,10-methylene tetrahydrofolate reductase have a widely varying biochemical outcome, they all have in common an elevated plasma homocysteine. Patients with these metabolic distur-
Hypercysteinophilic syndrome: endocardial fibrosis

SIR,—We were interested to read Pitt and colleagues' description of their patient with endocardial fibrosis.4 At the end of their discussion they mention that future management of their patient will involve assessment for cardiac transplantation. However, they do not mention endocardectomy, which we regard as the operation of choice in suitably symptomatic patients. The operation consists of endocardial decorticization, essentially a coring out of the fibrous tissue, with atrioventricular valve replacement or repair. We recently had a 40-year-old female Lebanese patient with endocardial fibrosis affecting both ventricles who underwent biventricular endocardectomy with tricuspid valve annuloplasty. Although she had a slow recovery requiring inotropic support for five days, and was eventually discharged on the 20th postoperative day, symptomatically she was much improved.

Endocardial decorticization for this disease was introduced by Dubost et al in 1973 and there are now several operative series in the literature.5 Most series report a hospital mortality rate of 20%, most often secondary to low cardiac output. For those who survive the operation 75% are alive after five years, and in the majority of cases there is good clinical improvement.6 Untreated patients, with endocardial fibrosis usually die within three years. Most patients in the reported series were in NYHA class III or IV and it is likely that operation mortality will be less if patients undergo surgery at an earlier stage.

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SIR,—We read with great interest the paper on endocardial fibrosis (EMF) by Rashwan et al.7 Their association of cases with hepatosplenic schistosomiasis, which was felt to be involved in the production of EMF rather than just the coincidence of two diseases, has been reported previously. We published a case report in 1973 making the suggestion of a pathogenetic relation of schistosomiasis to EMF.8 Another case report illustrating the association was published more recently.9

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Deterioration in renal function with enalapril but not losartan in a patient with renal artery stenosis by a solitary kidney

SIR,—Angiotensin-converting enzyme (ACE) inhibitors are widely used in the treatment of hypertension and heart failure. However, when given to patients with bilateral renal artery stenosis or unilateral stenosis in a solitary kidney, they can cause renal impairment that is usually reversible on stopping the drug. Recently, an angiotensin II (AII) receptor blocker (losartan) was introduced for the treatment of hypertension. We report a patient with severe hypertension and apparent heart failure who developed renal impairment with an ACE inhibitor but not with the AII receptor antagonist.

A 73-year-old man with a previous history of severe hypertension was admitted to hospital with symptoms and signs of biventricular failure. Blood pressure was 150/90 mmHg and apical heart rate was 148 beats/min on admission. A 36-year-old woman was referred to the emergency department with sustained atrial fibrillation. The patient was then started on losartan 50 mg twice daily in addition to two Frumil (co-amiloride 5/40). Soon after starting the treatment, the patient remained in atrial fibrillation which required cardioversion and anticoagulation with warfarin. The patient was then started on losartan 50 mg twice daily in addition to two Frumil (co-amiloride 5/40).