LETTERS TO THE EDITOR

Scope
Heart welcomes letters commenting on papers published in the journal in the previous six months. Topics not related to papers published earlier in the journal may be introduced as a letter: letters reporting original data may be sent for peer review.

Presentation
Letters should be:
- not more than 600 words and six references in length
- typed in double spacing (fax copies and paper copy only)
- signed by all authors.

They may contain short tables or a small figure. **Please send a copy of your letter on disk**. Full instructions to authors appear in the January 1997 issue of *Heart* (page 89).

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 B_{12} than healthy control subjects. There was not a 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 (tHcy) in patients compared with control subjects ($P = 0{\cdot}004$ and $P = 0{\cdot}003$).

Hyperhomocysteinaemia may emerge due to genetic factors, for instance from deficiency of the enzyme cystathionine β synthase (CBS), which participates in a transsulphuration pathway, or from thermolabile or mutant enzyme methylenetetrahydrofolate reductase (MTHFR) which synthesises 5-methyltetrahydrofolate, or from inborn errors of cobalamin transport and metabolism. Lower concentrations of vitamins B_{12}, B_6, B_2, cofactor form flavin adenine dinucleotide (FAD), or folate in serum or plasma may also be associated with hyperhomocysteinaemia. Vitamins B_{12}, B_6, and B_2 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.[2]

Miller and colleagues[3 4] have indicated that vitamin B_6 deficiency in humans or rats may not be associated with fasting hyperhomocysteinaemia. Fasting plasma tHcy concentrations in vitamin B_6 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 ($P = 0{\cdot}001$). During methionine loading, vitamin B_6 deficient rats exhibited a dramatic elevation of plasma tHcy concentrations which persisted for four hours or longer ($P < 0{\cdot}001$). Folate deficient rats did not show any significant increase in plasma tHcy.[3 4]

My colleagues and I have shown that serum folate and vitamin B_{12} concentrations had significant influence on fasting plasma tHcy concentrations; however; the influence of vitamin B_6 on fasting plasma tHcy was weak, probably due to smoking.[5]

These findings may indicate that homocysteine response during methionine loading may be different for folate or vitamin B_6 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 B_6 or heterozygote deficiency of CBS.

Therefore, it may be interesting to measure concentrations of vitamin B_6 in plasma or whole blood to investigate a potential role of vitamin B_6 in the development of hyperhomocysteinaemia in the Chinese patients. This might be important because patients with premature coronary artery disease had higher concentrations of folate in serum and erythrocytes. Measurement of vitamin B_2 in the serum from patients and control subjects may also add new information in the study.

M AZAM MANSOOR
Division of Clinical Chemistry, Central Hospital in Rogaland, 4003 Stavanger, Norway

1 Lolin YI, Sanderson JE, Cheng SK, Chan CF, Pang CP, Woo KS, Masarei JRL. Hyperhomocysteinaemia and premature coronary artery disease in the Chinese. *Heart* 1996;**76**: 117–22.
2 Ueland PM, Refsum H, Brattström L. Plasma homocysteine and cardiovascular disease. In: Francis RB Jr, ed. *Atherosclerotic cardiovascular disease, haemostatis, and endothelial function*. New York: Marcel Dekker, 1992: 183–236.
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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 our subjects. His suggestions about measuring B_6 and B_2 are very welcome. They are, however, based on the observations that the incidence of post-methionine hyperhomocysteinaemia, but not of fasting hyperhomocysteinaemia, was significantly higher in patients than in controls. The number of subjects in our study was small and, though not statistically significant, there was a difference between patients and controls regarding fasting hyperhomocysteinaemia (22% *v* 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 and indicated that low serum or plasma folate levels were associated predominantly with fasting hyperhomocysteinaemia, and B_6 deficiency or heterozygote deficiency of cystathionine β synthase (CBS) with post-methionine hyperhomocysteinaemia. Our study showed that in the Hong Kong Chinese, folate and B_{12} deficiencies were unlikely to be aetiologically important. This may have contributed to the relatively low incidence of, and modest fasting, hyperhomocysteinaemia. The striking response to methionine may well have been accounted for by heterozygous deficiency of CBS. Dietary deficiencies of B_6 and B_2, 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 B_6), asparagus (particularly B_2), spinach, and broccoli, all of which are eaten in abundance in this population throughout the year. A defective utilisation of these coenzymes 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.

YI LOLIN
Consultant in Chemical Pathology and Metabolic Medicine, Kent and Sussex NHS Trust, Kent and Sussex Hospital, Mount Ephraim, Tunbridge Wells, Kent TN4 8AT, United Kingdom

Homocysteinaemia and coronary atherosclerosis

SIR,—I read with great interest the article on hyperhomocysteinaemia and premature coronary artery disease in Hong Kong Chinese patients.[1] As suggested by the title of the accompanying editorial,[2] homocysteine has emerged as another risk factor for the development of coronary artery disease.

Homocysteine in human plasma arises solely from the breakdown of the essential amino acid methionine obtained only from dietary sources. Dietary homocysteine is complexed to various thiols, and does not appear under normal circumstances to influence plasma homocysteine.[3] 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 its remethylation to methionine.[4] 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 concentrations declining rapidly to the normal range. The study by Lolin and colleagues[1] suggests that in the Hong Kong Chinese patients hyperhomocysteinaemia was associated with genetically inherited abnormalities in enzymes associated with its metabolism.

Thus, while patients with reduced concentrations of cystathionine synthase, methionine synthase, or 5,10-methylene tetrahydrofolate reductase have a widely varying biochemical outcome, they all have in common an elevated plasma homocysteine.[3] Patients with these metabolic distur-

bances have one common clinical manifestation, namely, premature coronary artery disease. Patients with Down's syndrome have an additional copy of the gene that codes for cystathione synthase, thus giving them double the amount of this enzyme.[3] The result is that they have a much lower than normal homocysteine concentration. Patients with Down's syndrome have been noted as being remarkably free from coronary artery disease.

It has been over two decades since the publication of the original animal work of McCully and Wilson[5] who proposed the homocysteine theory of arteriosclerosis. After being ignored for many years, homocysteine has finally re-emerged as a risk factor for the development of human atherosclerosis. Although it is "the new player in the field of coronary risk",[2] homocysteine will become an increasingly important player that can no longer be ignored in the modern-day management of patients with coronary artery disease.

TSUNG O CHENG
Professor of Medicine,
The George Washington University,
Washington, DC 20037, USA

1 Lolin YI, Sanderson JE, Cheng SK, Chan CF, Pang CP, Woo KS, *et al.* Hyperhomocysteinaemia and premature coronary artery disease in the Chinese. *Heart* 1996;**76**: 117–22.
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This letter was shown to the authors, who reply as follows:

SIR,—Professor Cheng indicates that: (1) patients with genetic defects (cystathionine β synthase (CBS) and 5,10-methylenetetrahydrofolate reductase) have high plasma concentrations of homocysteine and premature coronary artery disease (CAD), as confirmed again by Lolin's paper; and (2) patients with Down's syndrome have a high CBS activity (the CBS gene is located on chromosome 21) and subsequently low concentrations of homocysteine resulting in a low incidence of CAD.

The high CBS activity and the low plasma concentration of homocysteine in Down's syndrome patients have been known for a long time[1–3] and, in 1977, Murdoch described Down's syndrome as a human model free from atheroma.[4] Thus, the remarks of Professor Cheng are correct, although not new. The remaining question is the possible causal relationship between the genetic abnormality and the weak incidence of CAD in Down's syndrome patients. The latter is still controversial because of the reduced life expectancy and other interfering factors. Finally, authors have also reported "normal" concentrations of homocysteine in Down's syndrome patients.[5] I think that we need more data to relate the gene abnormality to a low incidence of CAD in Down's syndrome patients.

G MONTALESCOT
Groupe Hospitalier Pitié-Salpêtrière,
47–83 Boulevard de l'Hôpital, 75651 Paris,
Cedex 13, France

1 Chadefaux B, Rethone MO, Raoul O, Ceballos I, Poissonnier M, Gilgenkranz S, *et al.* Cystathionine β synthase: gene dosage effect in trisomy 21. *Biochem Biophys Res Commun* 1985;**128**:40–4.
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Hypereosinophilic syndrome: endomyocardial fibrosis

SIR,—We were interested to read Pitt and colleagues' description of their patient with endomyocardial fibrosis.[1] 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 decortication, 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 endomyocardial fibrosis effecting 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 decortication for this disease was introduced by Dubost *et al* in 1973[2] and there are now several operative series in the literature.[3] 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.[3] Untreated, patients with endomyocardial fibrosis usually die within three years. Most patients in the reported series were in NYHA class III or IV and it is likely that operative mortality will be less if patients undergo surgery at an earlier stage.

JAMIL MAYET
PRAPA KANAGARATNAM
CHRISTOPHER LINCOLN
PAUL OLDERSHAW
Royal Brompton Hospital,
Sydney Street,
London SW3 6NP, United Kingdom

1 Pitt M, Davies MK, Brady AJB. Hypereosinophilic syndrome: endomyocardial fibrosis. *Heart* 1996;**76**:377–8.
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Endomyocardial fibrosis in Egypt: an illustrated review

SIR,—We read with great interest the paper on endomyocardial fibrosis (EMF) by Rashwan *et al.*[1] 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.[2] Another case report illustrating the association was published more recently.[3]

JH ANTONIO
MC DINIZ
D MIRANDA
HL SOARES
EJC MELO
Department of Internal Medicine,
Faculdade de Ciências Médicas Belo Horizonte,
Minas Gerais—Brazil
D MIRANDA
A NUNES
Department of Pathology,
Santa Casa de Belo Horizonte,
Minas Gerais—Brazil

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Deterioration in renal function with enalapril but not losartan in a patient with renal artery stenosis in 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.[1] 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 mm Hg and apical heart rate was 148 beats/min on treatment with digoxin 125 μg daily, frusemide 40 mg daily, enalapril 10 mg twice daily, nifedipine LA 30 mg daily, and warfarin. Serum creatinine was 308 μmol/l. Renal ultrasonography showed a small left kidney (8·9 cm) and a normal size right kidney. Echocardiography revealed concentric left ventricular (LV) hypertrophy, no valve lesions and good LV function.

Coronary angiography revealed an 80% diffuse disease of the left anterior descending artery, and a 50% obtuse marginal stenosis. Renal angiography performed at the same time revealed total occlusion of the left renal artery and a proximal severe stenosis of a single right renal artery (fig). Enalapril was therefore discontinued and five days later serum creatinine fell to 148 μmol/l.

Subsequently, blood pressure and symptoms of apparent heart failure were difficult to control despite adequate control of the atrial fibrillation. The patient was then started on losartan 50 mg twice daily in addition to two Frumil (co-amilofruse 5/40)