

## VIEWPOINT

# Hyperhomocysteinaemia, *Helicobacter pylori*, and coronary heart disease

J J Y Sung, J E Sanderson

Department of  
Medicine, Prince of  
Wales Hospital, The  
Chinese University of  
Hong Kong, Shatin,  
Hong Kong  
J J Y Sung  
J E Sanderson

Correspondence to:  
Dr J J Y Sung, Department  
of Medicine, Prince of Wales  
Hospital, The Chinese  
University of Hong Kong,  
Shatin, Hong Kong.

Accepted for publication  
12 March 1996

**Abstract**  
Hyperhomocysteinaemia and *Helicobacter pylori* infection have recently been implicated in the pathogenesis of coronary artery disease. These two risk factors, though they seem unrelated, could be linked by a deficiency of vitamins and folate caused by chronic gastritis in *H pylori* infection. This nutritional defect could lead to failure of methylation by 5-methyl-tetrahydrofolic acid and thus exacerbate the accumulation of homocysteine in susceptible patients. Homocysteine is toxic to endothelial cells and results in coronary artery disease.

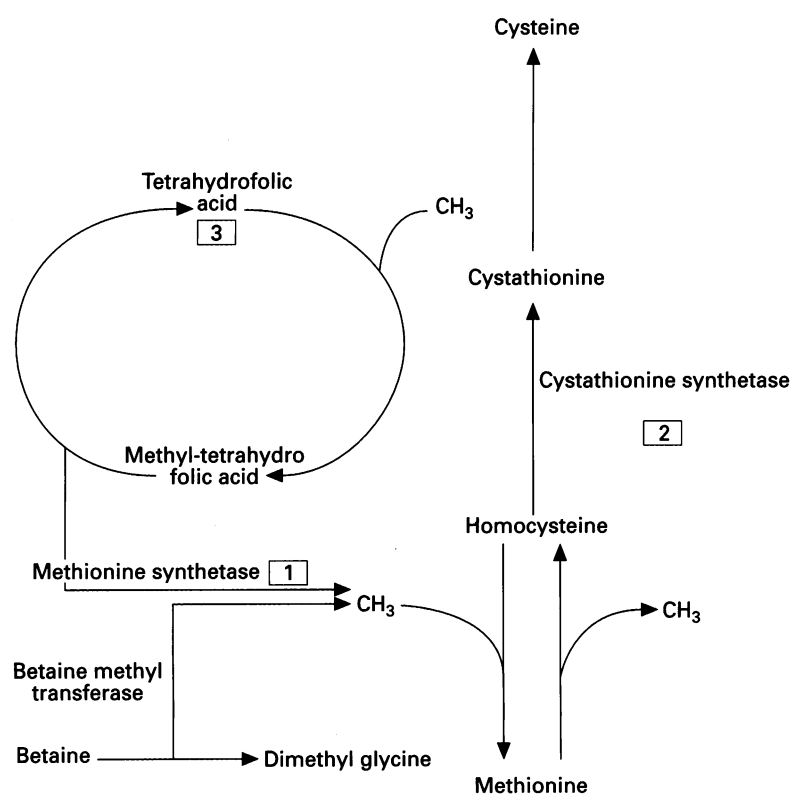
(Heart 1996;76:305-307)

Keywords: hyperhomocysteinaemia, *Helicobacter pylori*, coronary heart disease

Coronary artery disease causes high morbidity and mortality in almost every ethnic group. Conventional risk factors such as hyperlipidaemia, hypertension, and cigarette smoking do not account for all cases of coronary artery disease. Recently, many investigators have demonstrated that homocysteine concentrations are raised in adult patients with atherosclerosis and coronary, cerebral, and peripheral vascular diseases.<sup>1-3</sup> In addition *H pylori*, a bacterium causing chronic gastritis and peptic ulcers, has recently been associated with coronary heart disease.<sup>4</sup> Yet the mechanism by which *H pylori* infection leads to atherosclerosis is poorly understood. We propose a link between these two newly implicated risk factors in the development of coronary heart disease.

## Hyperhomocysteinaemia and coronary heart disease

Homocysteine is a thiol-containing amino acid produced by demethylation of methionine. Half of the homocysteine formed goes through the trans-sulphuration pathway and the other half takes a methyl group from betaine (betaine methyl-transferase) or 5-methyl-tetrahydrofolic acid (methionine synthetase) (fig 1). Methionine synthetase is a cobalamin-dependent enzyme which is functionally impaired when vitamin B-12 metabolism is abnormal. Homocysteinuria, an autosomal recessive condition, is usually caused by a deficiency of the enzyme cystathionine  $\beta$ -synthetase. This enzyme is required for the conversion of homocysteine to cystathionine. These patients have excessively high circulating concentrations of homocysteine resulting in a high risk of premature arteriosclerosis and venous thrombosis.<sup>5</sup> The mechanisms for the association of hyperhomocysteinaemia with atherosclerosis are still unclear. Animal studies have shown that homocysteine infusion causes epithelial damage.<sup>6</sup> Homocysteine is directly toxic to endothelial cells. It also inhibits the secretion of nitric oxide from endothelial cells and this action facilitates platelet aggregation and vasoconstriction.<sup>7</sup> Homocysteine may alter the balance between procoagulants and



- (1) Cobalamin dependent  
(2) Depends on intake and absorption  
(3) Pyridoxine dependent

Figure 1 Metabolism of homocysteine.

anticoagulants by selectively inhibiting the processing and secretion of thrombomodulin, reducing the activation of protein C, and inducing a protease activator of coagulation factor V.<sup>8</sup>

There have been reports of hyperhomocysteinaemia in adults (both white and Chinese patients) with premature coronary artery disease who lacked the other characteristics of homozygous homocystinuria.<sup>1-3</sup> This was attributed to a heterozygous defect in cystathionine synthetase production. The raised serum homocysteine concentration showed no correlation with increased plasma concentrations of cholesterol, low density lipoprotein, or triglyceride; cigarette smoking; and hypertension.<sup>9,10</sup> The odds ratios of hyperhomocysteinaemia for the development of coronary artery disease was 23.9. This is much higher than the risk of hypercholesterolaemia, hypertension, and cigarette smoking for myocardial ischaemia.<sup>1</sup> However, a very strong correlation was shown between poor vitamin intake or vitamin concentrations in plasma (especially vitamins B-6 and B-12 and folate) and hyperhomocysteinaemia.<sup>2,11</sup> As cobalamin is an essential cofactor for methionine synthetase and because in folate deficiency there is a lack of 5-methyl-tetrahydrofolic acid, deficiency of these vitamins results in further accumulation of homocysteine. Indeed, very high homocysteine concentrations have been reported in patients with vitamin deficiency, especially when multiple vitamin deficiencies were present.<sup>11,12</sup> Furthermore, vitamin supplementation can normalise homocysteine concentrations.<sup>13</sup>

#### *Helicobacter pylori* infection and coronary artery disease

*H. pylori* was first identified in patients with chronic gastritis as a Gram negative curved

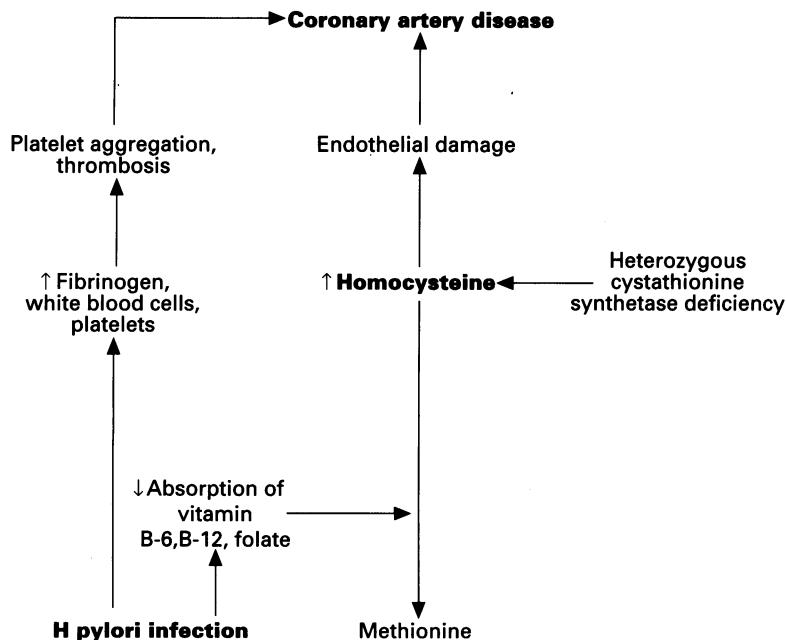


Figure 2 *H. pylori* infection, hyperhomocysteinaemia, and coronary artery disease.

bacillus.<sup>14</sup> After a decade of intensive research, the causal relation of this bacterium with peptic ulcer disease is widely accepted.<sup>15</sup> Recently, studies have suggested that chronic infection with *H. pylori* may be associated with the risk of coronary artery disease.<sup>4,16</sup> In a case-controlled study, it was found that seropositivity for *H. pylori* infection conferred a twofold risk of coronary heart disease.<sup>4</sup> Like hyperhomocysteinaemia, the association of *H. pylori* infection with coronary artery disease is independent of other conventional risk factors such as smoking, hypertension, and hyperlipidaemia.<sup>17</sup> A reverse causality—that is, that acute myocardial infarction causes a false positive serological test—is unlikely. *H. pylori* infection is acquired largely in childhood and there is no difference in antibody titre between patients with or without a history of previous myocardial infarction.<sup>17</sup> However, the possible mechanism of a chronic infection by *H. pylori* leading to atherosclerosis is not known. One hypothesis is that chronic infection accompanied by persistent inflammation increases the concentration of acute phase reactants, such as fibrinogen and sialic acid, which are predictors of coronary artery disease.<sup>18-20</sup> In a study by Patel *et al* fibrinogen concentration and total leucocyte count were higher in patients with cardiovascular disease and infected by *H. pylori*.<sup>17</sup> However, the increase in fibrinogen concentrations was not confirmed in another study.<sup>21</sup> *H. pylori* infection may have other peripheral effects outside the stomach that predispose to the development of heart disease.

#### *H. pylori* infection and nutritional deficiency

*H. pylori* infection can cause more than gastrointestinal diseases. It has been shown that *H. pylori* infection reduces stature in children, probably because of a nutritional effect of gastric inflammation on absorption.<sup>22,23</sup> In the elderly, *H. pylori* infection was associated with hypoalbuminaemia that was not explained by diet.<sup>24</sup> Because vitamin B-12 absorption depends on the secretion of intrinsic factors by the parietal cells, gastric dysfunction commonly causes a malabsorptive state. Patients infected by *H. pylori* causing gastritis have been shown to suffer from malabsorption of cobalamin.<sup>25</sup> Thus *H. pylori* infection can cause a nutritional deficiency, especially of vitamin B-6, vitamin B-12, and folate, and this will predispose to accumulation of homocysteine in heterozygotic patients. Furthermore, because *H. pylori* infection is frequently acquired in childhood and persists for long periods, a mild degree of nutritional deficiency may be present for many years and lead to the development of atherosclerosis.

#### Hypothesis (fig 2)

We propose that chronic *H. pylori* infection leads to malabsorption of vitamin B-6, vitamin B-12, and folate; failure of methylation; and hyperhomocysteinaemia. Homocysteine could

be responsible for the arterial damage associated with *H pylori* infection. This hypothesis, therefore, links two hitherto disparate and unexplained causes of coronary artery and peripheral vascular disease. This hypothesis should be readily amenable to testing by further studies.

- 1 Clarke R, Daly L, Robinson K, Naughten E, Cahalane S, Fowler B, *et al.* Hyperhomocysteinemia: an independent risk factor for vascular disease. *N Engl J Med* 1991; 324:1149-55.
- 2 Stampfer MJ, Malinow MR, Willet WC, Newcomer LM, Upson B, Ullmann D, *et al.* A prospective study of plasma homocysteine and risk of myocardial infarction in US physicians. *JAMA* 1992;268:877-81.
- 3 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.
- 4 Mendall MA, Goggin PM, Molineaux N, Levy J, Toosy T, Strachan D, *et al.* Relation of *Helicobacter pylori* infection and coronary heart disease. *Br Heart J* 1994;71:437-9
- 5 Grieco AJ. Homocystinuria: pathogenic mechanisms. *Am J Med Sci* 1977;273:120-32.
- 6 Harker LA, Slichter SL, Scott CR, Ross R. Homocystinemia: vascular injury and arterial thrombosis. *N Engl J Med* 1974;291:537-43.
- 7 Stamler JS, Osborne JA, Jaraki M, Rabbini LE, Mullins M, Singel D, *et al.* Adverse vascular effects of homocysteine are modulated by endothelium-derived relaxing factor and related oxides of nitrogen. *J Clin Invest* 1993;91: 308-18.
- 8 Wu LL, Wu J, Junt SC, James BC, Vincent GM, Williams RR, *et al.* Plasma homocysteine as a risk factor for early familial coronary artery disease. *Clin Chem* 1994;40: 552-61.
- 9 Murphy-Chutorian DR, Wexman MP, Grieco AJ. Methionine intolerance: a possible risk factor for coronary artery disease. *J Am Coll Cardiol* 1985;6:725-730.
- 10 Kang SS, Wong PWK, Cook HY, Norusis M, Messer JV. Protein-bound homocysteine—a possible risk factor for coronary artery disease. *J Clin Invest* 1986;77: 1482-6.
- 11 Ubbink J, Vermaak W, Van der Merwe A, Becker P. Vitamin B12, vitamin B6 and folate nutritional status in men with hyperhomocysteinemia. *Am J Clin Nutr* 1993; 57:47-53.
- 12 Stabler SP, Marcell PD, Podell ER, Allen RH, Savage DG, Lindenbaum J. Elevation of total homocysteine in the serum of patients with cobalamin or folate deficiency detected by capillary gas chromatography-mass spectrometry. *J Clin Invest* 1988;81:466-74.
- 13 Dudonan NP, Wilcker DE, Wong J, Lynch JF, Macey D, Lundberg P. Disordered methionine/homocysteine metabolism in premature vascular disease. Its occurrence, cofactor therapy, and enzymology. *Arterioscler Thromb* 1993;13:1253-60.
- 14 Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984;ii:1311-5.
- 15 NIH Consensus Development Panel. *Helicobacter pylori* in peptic ulcer disease. *JAMA* 1994;272:65-9.
- 16 Martide-de-Argila C, Boixeda D, Fuertes A, Canton R, Barba M, Gisbert JP, *et al.* *Helicobacter pylori* infection and coronary heart disease. *Gut* 1995;37(suppl 1):A25.
- 17 Patel P, Mendall MA, Carrington D, Strachan DP, Leatham E, Molineaux N, *et al.* Association of *Helicobacter pylori* and *Chlamydia pneumoniae* infections with coronary heart disease and cardiovascular risk factor. *Br Med J* 1995;311:711-4.
- 18 Yarnell JW, Baker IA, Sweetnam PM, Bainton D, O'Brien JR, Whitehead PJ, *et al.* Fibrinogen, viscosity and white blood cell count are major risk factors for ischemic heart disease. The Caerphilly and Speedwell collaborative heart disease studies. *Circulation* 1991;83:836-44.
- 19 Meade TW, Brozovic M, Chakrabarti RR, Haines AP, Imeson JD, Mellows S, *et al.* Haemostatic function and ischemic heart disease: principal results of the Northwick Park heart study. *Lancet* 1986;ii:533-7.
- 20 Lindberg G, Eklund GA, Gullberg B, Rastam L. Serum sialic acid concentration and cardiovascular mortality. *Br Med J* 1991;302:143-6.
- 21 Murray LJ, Bamford KB, Reilly DPJ, McCrum EE, Evans AE. *Helicobacter pylori* infection: relation with cardiovascular risk factors, ischemic heart disease and social class. *Br Heart J* 1995;74:497-501.
- 22 Raymond J, Bergeret M, Benhamou PH, Mensah K, Dupont C. A two-year of *H. pylori* infection in children. *J Clin Microbiol* 1994;32:461-3.
- 23 Mendall MA, Molineaux N, Levi J, Strachan D, Northfield TC. Association of *H. pylori* with diminished adult height. *Gastroenterology* 1994;106:A137.
- 24 Wong BCY, Ching CK, Lam SK, Lai KC, Hu WHC, Ong LY, *et al.* Association of *Helicobacter pylori* infection with hypoalbuminaemia and dietary habits. *Gastroenterology* 1995;108:260A.
- 25 Carmel R, Perez-Perez GI, Blaser MJ. *Helicobacter pylori* infection and food-cobalamin malabsorption. *Dig Dis Sci* 1994;39:309-14.