Early Descriptions of Possible Angina Pectoris

Notwithstanding the conditions prevailing before the eighteenth century, there were undoubtedly some few individuals who had the potential for development of ischaemic heart disease. This can occur in the absence of exogenous risk factors for coronary arteriosclerosis, for example, in rare homozygous subjects with familial abnormalities of cholesterol metabolism.[3] Congenital coronary arterial anomalies can also very occasionally cause angina independently of arteriosclerotic disease.[4] Either of these could have accounted for Heberden's twelve-year-old patient with exertional chest pain. The present work does not therefore attempt to prove that angina pectoris was a totally new syndrome emerging in the mid-eighteenth century in the way, for example, that Acquired Immune Deficiency Syndrome (AIDS) first became manifest in the late 1970s. It *is* being suggested that before the mid-eighteenth century angina pectoris was too rare to have been recognisable as a distinct clinical entity by any one physician.

Coronary Heart Disease Frequency in the Absence of Traditional Risk Factors

In mid-twentieth century studies, the frequency of symptomatic coronary heart disease occurring in the then apparent absence of risk factors may have been overestimated. When the association of lipid abnormalities with increased risk of coronary arterial disease was first recognized, "normality" of serum cholesterol was based on results of measurements that were made in apparently healthy subjects. Levels that were then accepted as normal would now be regarded as pathologically high and a consequence of the excessively fatty diets and possibly resulting obesity that has been all too common in western societies. As late as 1998, the CARE study, an investigation of the effect of pravastatin (a cholesterol lowering medication) on the incidence of coronary events among survivors of a first myocardial infarction was initiated because total serum cholesterol levels in the range of 5.2 to 6.2 mmol/L were then considered to be unproven as risk factors and therefore regarded as normal. Indeed the ethical decision to allow randomizing half the study population to placebo treatment was based on this premise. The term hypercholesterolaemia was reserved for levels above 6.2 mmol/L. The results of the CARE study itself showed that serum cholesterol concentrations earlier categorized as "average" should now be considered pathologically high, even 5.2 mmol/L being considered excessive.[5]

A measure of the incidence of overt coronary heart disease in populations with total serum cholesterol levels that are acceptable as normal by present standards

[3] Peter H Jones and Antonio M Gotto, 'Assessment of lipid abnormalities in the heart', in J Willis Hurst and Richard C Schlant (eds), *The heart, arteries and veins*, 7th ed., New York, McGraw Hill, 1990, p. 378.

[4] J Noble *et al.*, 'Myocardial bridging and milking effect of the left anterior coronary artery. Normal variant or obstruction?', *Am J Cardiol*, 1976, **37**: 993–9, p. 997.

[5] F M Sacks *et al.*, 'Relationship between plasma LDL concentrations during treatment with pravastatin and recurrent coronary events in the Cholesterol and Recurrent Events trial', *Circulation*, 1998, **15**: 1446–52, p. 1447.

can be derived from a number of epidemiologic studies. Among the most valuable is the MRFIT study which involved a six-year follow-up of over one-third of a million American males who were between thirty-five and fifty-seven years of age at entry and free of known coronary heart disease. The published results include reports of CHD death rates among a subgroup of men who did not smoke cigarettes and had low serum total cholesterol levels. This would have a direct bearing on circumstances that prevailed before the beginnings of the Agricultural Revolution when diets were perforce deficient in animal fats and cigarettes unknown. There were 45,353 such men in the MRFIT study who had initial total serum cholesterol levels below 4.68 mmol/L. Of these, 83 died as a result of coronary heart disease, a yearly rate of about 0.30 per thousand.[6] The United States findings have been paralleled by observations in China where Zhenming Chen and his colleagues studied 6,494 men and 2,857 women. They were observed for eight to thirteen years and their ages ranged from thirty-five to sixty-four years at recruitment. In a 2,162 subsection of these subjects the initial total serum cholesterol was below 3.53 mmol/L, their mean being 3.08. During the period of observation, there were four coronary heart disease deaths, which, assuming an average follow-up of about ten years, gives a death rate of roughly 0.18 per thousand per year.[7] Although smokers were not excluded from the study, this incidence is little more than half the rate observed in the USA investigation, the lower initial serum cholesterol level used to define the Chinese group possibly accounting for the difference. Both the MRFIT and the Chinese studies were initiated before treatment had made any appreciable impact on mortality. They both suggest therefore that a population living before the onset of the Agricultural Revolution and having perforce a low fat diet could well have been subject to comparable death rates from coronary heart disease, i.e. between 0.18 and 0.30 per thousand per year.

These low incidence rates suggest that when the serum total cholesterol levels are low, other recently recognised risk factors have little epidemiological significance (see page 74). As an example, Meir Stampfer and others conducted a *prospective* study of the relation of plasma homocysteine levels to risk of myocardial infarction. This amino acid is associated with premature arterial disease when present in excess. In what ultimately proved to be a low risk group generally, 14,916 male American physicians aged forty to eighty-four years at entry and with no prior infarction or stroke were followed for five years. Among patients with homocysteine levels in the 95th upper percentile or higher there were thirty-one cases, scarcely 0.2 per cent of the total population at risk.[8] Lp(a) also appears to be of doubtful importance as a risk factor when other lipid levels are low.[9] The same is true of coagulation and

[6] Jeremiah Stamler, Deborah Wentworth and James D Neaton, 'Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded?', *JAMA*, 1986, **256**: 2823–8, p. 2825.

[7] Zhenming Chen *et al.*, 'Serum cholesterol and coronary heart disease in a population with low cholesterol concentrations', *Br Med J*, 1991, **303**: 276–82, p. 279.

[8] Meir Stampfer *et al.*, 'A prospective study of plasma homocyst(e)ine and risk of myocardial infarction in US physicians', *JAMA*, 1992, **268**: 877–81, p. 879.

[9] Bernard Cantin *et al.*, 'Is lipoprotein (a) an independent risk factor for ischemic heart disease in men? The Quebec cardiovascular study', *J Am Coll Cardiol*, 1998, **31**: 519–25, p. 521.

clotting functions. Thus G J Miller and co-workers found that when fat intake is low factor VII concentration is reduced[10] and in addition the impact of fibrinogen on CHD incidence has been found to be lower when serum LDL cholesterol levels are relatively low.[11]

If the 0.18 to 0.30 per thousand annual mortality reported in the Chinese and MRFIT studies is any indication, other manifestations of CHD such as angina pectoris could also be presumed to have been infrequent. A general physician would need to wait for years and see several thousand patients before finding a single case. This would have been the situation of the eighteenth-century doctor who was a general practitioner in the fullest sense, attending adults and children, men and women, young and old, victims of trauma, and patients with psychiatric as well as organic diseases. Recognition of a distinctive syndrome requires seeing, preferably not too far apart in time, some minimum number of patients with similar clinical features. Before 1768 Heberden saw patients with the typical chest pain on exertion with a frequency that averaged about once a year, and it was only after he had experience of a total of twenty that he could group these subjects together, showing as they did common features of a condition concerning which he "could find no satisfaction from books".[12] It is therefore understandable that a much greater rarity of angina pectoris in an earlier era could have precluded its recognition as a distinct condition by even the most observant of clinicians.

Pathological Evidence of Coronary Arterial and Heart Disease before 1768

Arterial calcification has been described in Egyptian mummies, the earliest about thirty-five centuries old and the most notable that of the Pharaoh Menephtah. The incidence is of course unknown and observations were confined for the most part to the large arteries and to the aorta in particular.[13] Arteriosclerosis however is now known to be a diffuse process and the association of aortic with coronary arterial calcification is well recognized. Moreover, fibrous thickening of coronary arterial walls has been reported in a 3,000-year-old female mummy,[14] and "roughened" arteries were described in Bonet's *Sepulchretum* in 1679.[15] Twenty-nine years later "ossification" was observed in the coronary arteries by Thebesius, better known for the eponymously named veins and valves in the heart.[16] Coronary arterial

[10] G J Miller *et al.*, 'Fat consumption and factor VII coagulant activity in middle aged men. An association between a dietary and thrombogenic coronary risk factor', *Arteriosclerosis*, 1989, **78**: 19–24, p. 21.

[11] Jürgen Heinrich *et al.*, 'Fibrinogen and factor VII in the prediction of coronary risk. Results from the PROCAM study in healthy men', *Arterioscler Thromb*, 1994, **14**: 54–9, p. 56.

[12] William Heberden, 'Some account of a disorder in the breast', *Med Trans Coll Physns Lond*, 1772, **2**: 59–67, pp. 59–64, 62.

[13] H T Blumenthal (ed.), *Cowdry's arteriosclerosis: a survey of the problem*, 2nd ed., Springfield, ILL, Thomas, 1967, p. 6.

[14] Allen R Long, 'Cardiovascular renal disease. Report of a case three thousand years ago', *Arch Pathol*, 1931, **12**: 92–4.

[15] T Bonet, *Sepulchretum sive anatomia practica ex cadaveribus morbo denatis*, Geneva, Chouët, 1679, p. 387.

[16] J O Leibowitz, *The history of coronary heart disease*, London, Wellcome Institute of the History of Medicine, 1970, p. 74.