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.

"encrustations" were described in 1740 by Johann Crell,[17] and W Cowper, who lived from 1669 to 1709, speculated that coronary arterial blood flow could become impeded.[18] The seventeenth- and early eighteenth-century pathological descriptions have been summarized by J O Leibowitz.[19]

These early descriptions of what was apparently coronary arterial calcification and sclerosis might be considered indicative of coronary heart disease having existed before the mid-eighteenth century, even if of unknown prevalence and the consequences unrecognized clinically. There is, however, recent evidence to show that calcification in coronary arterial walls is not necessarily indicative of luminal stenosis or obstruction sufficient to cause symptomatic myocardial ischaemia. Calcification has been found at autopsy to extend over about 8 per cent of the aorta and the coronary arteries of black Jamaicans thus examined and in a similar percentage of both Guatemalan Indians and Durban Bantu, yet in all of these groups clinically overt coronary arterial disease is virtually unknown.[20] J N Morris reviewed London Hospital autopsy records of the early years of the twentieth century and found that coronary arteriosclerosis was then extensive.[21] It was a period when symptomatic coronary heart disease was very rare among the deprived social classes living in the catchment area of the hospital. Sclerotic coronary arterial changes and the chest pain of myocardial ischaemia were apparently dissociated.

The strongest evidence suggesting that coronary arterial anatomic changes and frequency of overt clinical coronary arterial disease can be disparate is provided by recent studies showing the effect of serum cholesterol reduction on pathological coronary arterial anatomy on the one hand and the incidence of symptomatic ischaemic heart disease on the other. In a Dutch study it was found that following successful lowering of serum cholesterol any changes in coronary arterial lumen diameter at the point of narrowing by plaque were measured in as little as hundredths of a millimetre, but the number of cardiac events was almost halved.[22] The results of twelve similar trials were reviewed by Gilbert Thompson. Following lipid-lowering therapy quantitative serial angiography showed that evidence of coronary arterial plaques persisted and may even have worsened, albeit less in treated than untreated patients. However, epidemiologic studies of the same patients demonstrated a dramatic reduction in the incidence of symptomatic coronary arterial disease that became evident within months.[23] D Sutton and R G Grainger observed that "radiologically visible coronary artery calcification in persons over 40" plays no significant

[17] Johann F Crell, 'Dissertatio de arteria coronaria instar ossis indurata observatio 1740', in A Haller, *Disputationes ad morborum historiam et curationem facientes. Vol II, Ad morbos pectoris*, Lausanne, M M Bousquet, 1757, p. 565.

[18] Leibowitz, op. cit., note 16 above, p. 113.

[19] Ibid., pp. 70–1.

[20] Jeremiah Stamler, 'Epidemiology of coronary heart disease', *Med Clin N Am*, 1973, **57**: 5–46, p. 14.

[21] J N Morris, 'Recent history of coronary disease', *Lancet*, 1951, i: 69–73, p. 71.

[22] J Wouter Jukema *et al.*, 'Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels', *Circulation*, 1995, **91**: 2528–40, p. 2534.

[23] Gilbert R Thompson, 'Angiographic trials of lipid-lowering therapy: end of an era?', *Br Heart J*, 1995, **74**: 343–7, p. 345.

part in the diagnosis of coronary heart disease.[24] Richard Frink and his colleagues found that at autopsy moderate degrees of calcification were often present in absence of significant stenosis.[25] Giuseppi Sangiorgi and his colleagues quantified coronary artery calcium at autopsy by contact microradiography while morphologic coronary artery integrity was maintained by perfusion at physiological pressures. They too found that throughout the entire range there was very poor correlation between the extent of calcification and the amount of reduction in luminal diameter.[26]

Two reasons for the discrepancy between the presence of coronary calcification and the absence of symptomatic coronary heart disease have been postulated. Firstly, degenerative changes in the arterial wall are often associated with weakening and consequent dilatation of the vessel, so that the calcified plaques project outwardly rather than into the lumen which consequently retains its size. Secondly, lipids are absorbed from cholesterol-rich and unstable plaques when serum lipid levels are reduced, whether by diet restriction, medication or both. Whilst calcific changes persist, fat-laden plaques become fibrous with stabilization of the previously fragile overlying cap. These developments, which have been observed directly in animal studies, minimize the successive risk of plaque fracture, extrusion of lipid into the lumen of the coronary artery, clot formation with blockage, and organization with subsequent increasing narrowing of the vessel, should the patient survive the episode. Persistent calcification is not therefore necessarily indicative of either flow-limiting arterial stenoses or potential for blood vessel occlusion by clot.[27]

Leibowitz has reviewed the pathological descriptions prior to the mid-eighteenth century that have been interpreted as evidence of myocardial infarction, but in many of these the evidence is inconclusive. Seventeenth- and eighteenth-century pathological descriptions, when available, are often difficult to recognize as myocardial infarction, examples being references to polyps, ulcers or "tubercles".[28] Solid substances found in the left ventricular cavity were probably clots. However, the distinction between antemortem and postmortem thrombi had not been recognized by the eighteenth century and clots in the left ventricular cavity can be associated with conditions other than myocardial infarction. More suggestive of an infarct are descriptions of cardiac rupture as cited by William Harvey in a letter to Professor Riolan of Paris and in accounts by Giovanni Battista Morgagni and S F Morand. Certainly in Harvey's patient and that of Morgagni, the rupture could have complicated a

[24] D Sutton (ed.), *A textbook of radiology and imaging*, 3rd ed., London, Churchill Livingstone, 1980, p. 491.

[25] Richard J Frink *et al.*, 'Significance of calcification of the coronary arteries', *Am J Cardiol*, 1970, **26**: 241–7, p. 244.

[26] Giuseppi Sangiorgi *et al.*, 'Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using non-decalcifying methodology', *J Am Coll Cardiol*, 1998, **31**: 126–33, p. 130.

[27] B Greg Brown *et al.*, 'Lipid lowering and plaque regression. New insights into prevention of plaque disruption and clinical events in coronary disease', *Circulation*, 1993, **87**: 1781–9, p. 1782.

[28] Leibowitz, op. cit., note 16 above, pp. 77ff.

myocardial infarction.[29] However, cardiac rupture as described in the eighteenth century must sometimes have been an entity different from the current one. Of the mere half dozen cases documented by Leibowitz, two involved the *right* ventricle, one incidentally resulting in the sudden demise of King George II.[30] In an era in which rheumatic heart disease was prevalent, infections common and bacterial endocarditis incurable, myocardial abscesses were a possible cause of cardiac rupture. Morgagni did describe a single case in which a tendinous left ventricular wall suggested presence of scarring as a sequel of myocardial infarction and his finding of a left ventricular aneurysm in another autopsy could imply a similar cause.[31] In both of these instances the victims must have survived the episode by months, if not years. An autopsy reported by Crell stands alone in describing an intracoronary soft yellow-white body which could be extruded. It had a worm-like form and the part of the heart through which this artery passed was withered and pulpy.[32] The description is compatible with either a thrombosis or with extruded contents of a ruptured soft atheromatous lesion, but it stands alone. Although most of these pathological reports were preceded by short clinical descriptions, none made reference to chest pain on effort.

In conclusion, thousands of pathological reports concerning the heart were extant from the period under consideration, notably, but not exclusively, in the writings of Bonet, Crell and Morgagni. The findings reviewed suggest that among them there were just seven autopsy descriptions that might be ascribed to myocardial infarction and that antedated Heberden's 1768 description of angina. Among the multitude of clinical descriptions accompanying the autopsy reports there were but two mentions of pain recognizable as angina pectoris having been a feature of the preceding illness, both by Morgagni and described in Chapter III. It must be noted too that in an era in which valvular disease of the heart and its infective complications were both probably much more prevalent than today, emboli, either sterile or infected, could have been the cause of myocardial infarction (although not angina of effort) with far greater relative frequency than is currently the case. Of the handful of pathological descriptions compatible with myocardial infarction that were recorded before 1768, none is necessarily secondary to coronary arterial disease.

Aortic and Coronary Ostial Stenoses

Aortic valve stenosis can cause angina pectoris in the absence of coronary arterial disease, but is very much rarer than coronary arteriosclerosis. It was probably less common still before the mid-eighteenth century. Arthur Boon and his colleagues and William Roberts found that risk factors for aortic stenosis included both raised

[29] William Harvey, *Exercitatio anatomica, de motu cordis et sanguinis in animalibus*, Rotterdam, Arnold Leers, 1648, pp. 99–102, 82; Giovanni Battista Morgagni, *The seats and causes of diseases*, transl. Benjamin Alexander, 3 vols, London, A Miller and T Cadell, 1769, vol. 1, Letter xxvii, p. 846; S F Morand, 'Sur quelques accidents remarquables dans les organes de la circulation du sang', *Mémoires de l'Académie Royale des Sciences*, 1732, p. 428–34.

[30] Leibowitz, op. cit., note 16 above, p. 82.

[31] Morgagni, op. cit., note 29 above, p. 846.

[32] Crell, op. cit., note 17 above, p. 565.