Although angina pectoris had been well known for many years, it was not until early in the 20th century that what we now term myocardial infarction seems to have been recognized. Thus, Herrick\(^1\) used the term 'coronary thrombosis' in 1912. The condition appears to have remained something of a clinical rarity until after the First World War, when mortality from it began to rise, some of which may have been due to diagnostic fashion but most of which was probably real. The increase in smoking among men during the war may have been largely responsible. The continuing rise in mortality after the Second World War stimulated a growing volume of research. Pathological studies systematically confirmed the fatty nature of atheromatous plaques and thus directed attention mainly towards the lipid infiltration hypothesis for coronary heart disease (CHD), particularly in the US. With the benefit of hindsight, this emphasis, virtually to the exclusion of Rokitansky's encrustation hypothesis involving the incorporation of microthrombi, may have caused significant delay in a fuller understanding of the pathology of CHD and thus of measures to reduce its incidence and recurrence. In fact, the part played by microthrombi in the pathology of arterial disease had recently been considered by Duguid,\(^2\) as Morris acknowledged in his extraordinarily imaginative and perceptive paper in 1951.\(^3\) Nevertheless, the predominant American view on the role of lipids was mainly reflected in the development of epidemiological studies and later in trials of dietary interventions designed to lower cholesterol levels. Morris's paper\(^3\) was entitled 'Recent History of Coronary Disease' and its great

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**Cardiovascular disease—linking pathology and epidemiology**

TW Meade

**Background**

Coronary heart disease (CHD) in the form of myocardial infarction first came to attention early in the 20th century. Mortality from CHD increased dramatically after the First World War and had assumed epidemic proportions, particularly in the USA, by 1945. The ensuing research stemmed almost exclusively from the lipid infiltration hypothesis for atheroma.

**Methods**

Using epidemiological methods, pathological evidence for the thrombotic component of CHD was demonstrated by Morris as early as 1951. Morris's main work was based, first, on routine autopsy records at the London (now Royal London) Hospital and, second, on the National Necropsy Survey relating physical activity at work to pathological findings.

**Results**

The indications from Morris's work that thrombosis contributes as much to clinical CHD as atheroma were in due course strengthened by the findings of clinical trials of aspirin, prospective studies incorporating measures of haemostatic function and further studies of pathology.

**Conclusions**

Recognition of the thrombotic contribution to CHD does not materially alter approaches to prevention through lifestyle modifications but does have major implications for pharmacological measures. Thus, aspirin and thrombolytic therapy are mandatory in the acute stage of suspected myocardial infarction while aspirin is also part of accepted practice in the longer term in secondary prevention. The value of warfarin is being rediscovered, often at a lower and therefore safer intensity of anticoagulation than previously considered necessary. The effect that warfarin may have on the vessel wall as well as on occlusion of the lumen is helping to reconcile the two major hypotheses for the pathology of CHD. Much of our current knowledge about the origins, management and prevention of CHD stems from Morris's early studies linking pathology and epidemiology.

**Keywords**

Atheroma, coronary heart disease, thrombosis

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importance has been matched only by the extent to which it seems to have been overlooked, certainly at the time.

Morris started by pointing out that before the First World War, the pathology department of the London (now Royal London) Hospital had one or two autopsies a year with a diagnosis of recent coronary thrombosis and/or acute myocardial infarction. However, an average of 3.6 per annum in 1907–1914 rose to 10.5 in 1944–1949, with considerably more men than women contributing. Over virtually the same period, the prevalence of advanced atheroma in men aged between 30 and 70 was 30.4% in 1908–1913 and 16.0% in 1944–1949 and death rates from CHD nationally had risen dramatically (Figure 1). The thrombotic contribution to the pathology of CHD appeared to have been at least as important as that of atheroma in explaining what had happened. ‘Oclusion is crucial in determining the transition from the merely pathological to the clinical’ as Morris put it and ‘perhaps advanced atheroma provides the basis, is the predisposing factor; but what will precipitate the heart-disease, who of the many so predisposed will develop the thrombosis/occlusion, and when, may not be a function simply and directly of the atheroma or of its severity’. Morris considered the blood’s coagulability and local disturbances of the affected vessel as providing ‘the setting and opportunity for the clotting’ and the proposition that ‘coronary thrombosis is the central problem’. He went on to comment on ‘the possibility that thrombus has been dissolved’ (citing MacFarlane and Biggs, two of the day’s leading experimental and clinical haematologists) to explain the apparently puzzling finding in many autopsies of occlusion ‘merely by stenosis’ without thrombosis. Most of the lifestyle characteristics now considered to contribute to CHD were at least mentioned by Morris and prevention through measures to reduce both atheroma and thrombotic potential was also raised. Any new recruit to the CHD research field would not be far behind others if he or she confined attention only to the 1951 paper and they would have the advantage of a far more stimulating background to account for its pathology than in most other texts.

In 1958, Morris and Crawford\(^5\) consolidated the evidence—if indeed this was necessary—that there are two main pathologies in CHD. Morris et al.\(^6\) had previously shown that London bus drivers experienced a higher sudden death rate from ‘coronary thrombosis’ than conductors and that government clerks did so more frequently than postmen. These and other studies led to the hypothesis that men in physically active jobs had a lower incidence of CHD than those in physically inactive jobs. The National Necropsy Survey\(^5\) collected data in a standard form from about 90% of the country’s 206 hospital pathologists on the degree of vessel wall changes, lumen occlusion and changes in the myocardium of 5000 consecutive autopsies in the mid-1950s on men aged 45–74, whatever the cause of death. Details of each man’s last occupation were obtained either from the pathologists or from the General Register Office (as what is now the Office of National Statistics was then known) and its physical activity coded as light, medium or heavy. The study was carried out in the days when many had still been in jobs truly involving physical exertion. The results were summarized ‘atheroma of coronary walls, no relationship with physical activity of occupation; occlusion of coronary lumen, some relationship; ischaemic myocardial fibrosis, much relationship’ the last in fact indicating infarction (Figure 2). At the time, the question as to whether those at different risks of CHD were selecting themselves into jobs because of their activity level had not been resolved. Nonetheless, the observation even then that activity had little or nothing to do with atheroma but a clear effect on thrombosis and infarction made it difficult to escape the conclusion that activity (or, conceivably, some other characteristic associated with it) was having very different effects on atherogenesis on the one hand, and thrombosis and infarction on the other—again, evidence of two major and largely distinct pathologies. Most now agree on a direct protective effect of exercise which does, of course, owe a great deal to Morris’s later work as well.\(^7\) The observation that vigorous exercise has to be

**Figure 1** Trends in CHD death rates and in prevalence of atheroma. A (right-hand scale), male death rates per 100 000 at ages 30–70 years in England and Wales. B (left-hand scale), age-standardized prevalence, per cent, of advanced coronary atheroma in males at ages 30–70 years in 1908–13 and 1944–49 (Morris 1951)

**Figure 2** Prevalence of different pathological manifestations of CHD according to physical activity of occupation (Morris & Crawford 1958, reproduced by permission of Update)
maintained to exert its benefit fits in with the 1958 National Necropsy Survey result—that it seems to work through short-term effects such as the level of coagulability thus influencing thrombotic potential, whatever effects it may also have on other pathways.

Illustrative of the emphasis placed by Morris on ‘completing the clinical picture’ was the study by Crawford and Morris in 1969 showing the ‘by no means rare’ occurrence of ruptured ventricle predominantly seen by coroners and much less often in hospital.

Epidemiological research after the Second World War was led and dominated by work in the US, notably the Framingham Study which, at least to begin with, paid virtually exclusive attention to the lipid infiltration hypothesis and what happens over years or decades in the vessel wall rather than to changes—as well—in the vessel lumen over hours or minutes. The emergence of ‘atherosclerosis’ and ‘atherosclerotic heart disease’ as terms to encompass both pathological and clinical manifestations of CHD did nothing to redress the balance—an etymological problem that still persists by drawing attention to disease’ as terms to encompass both pathological and clinical emergence of ‘atherosclerosis’ and ‘atherosclerotic heart—as well—in the vessel lumen over hours or minutes. The over years or decades in the vessel wall rather than to changes attention to the lipid infiltration hypothesis and what happens and dominated by work in the US, notably the Framingham ventricle predominantly seen by coroners and much less often of haemostatic function considered likely to influence the thrombogenic process alongside risk factors that were by then increasingly recognized—smoking and raised blood pressure and blood cholesterol levels. The first of these to report was the Northwick Park Heart Study, showing that high plasma fibrinogen levels, in particular, and possibly of other clotting factors and also impaired fibrinolytic activity independently contributed to the risk of subsequent CHD. Morris’s early work on pathology had been the main stimulus to this particular study. Without going into further detail, it is now clear that overactivity of the coagulation system and impaired fibrinolytic activity exert a major influence on thrombogenic potential and thus on the clinical manifestations of CHD. The second development, but with earlier results than those from the prospective studies, was the publication in the mid-1970s of laboratory studies and, in particular, of the earliest trials demonstrating the value of aspirin in secondary prevention, i.e. the prevention of recurrent events. Apart from the obvious clinical value of this reduction of some 25%, these trials confirmed the central role of platelets in CHD. When interest in the thrombotic component of CHD had begun to receive attention, most interest focused on platelets because of histological evidence of their involvement and also because of the rapidity of platelet aggregation following vessel wall injury. By contrast, the coagulation system was generally viewed as less exciting, possibly because it was also considered to be slower—although it later became clear that thrombin, the main functional product of coagulation, exerts its first effects on platelets. However, attempts to characterize those at risk on account of increased platelet sensitivity have proved unsuccessful. Indeed, there is still no validated test indicating the risk of first episodes because of this characteristic (although platelet size and spontaneous platelet aggregation may be associated with the risk of recurrence).

Further advances in pathology were a third development. The use of angiography in the early days of thrombolytic therapy put the sequence of thrombosis causing myocardial infarction beyond reasonable doubt and a few years later particularly careful autopsy studies showed a degree of thrombosis in nearly all cases of sudden death from CHD. The striking increase in fibrinolytic activity accompanying sudden death explains why thrombi that have probably been involved in leading to it often cannot be found at autopsy (referred to earlier).

It turns out that attributes such as smoking, dietary habit and physical activity all influence one or more of the haemostatic variables shown to be associated with CHD in directions that are to be expected if the latter do contribute to clinical events—for example, smoking increases and physical exertion decreases the plasma fibrinogen level. Dietary intake and blood lipids strongly influence coagulability. So knowing about the thrombogenic pathways in CHD has no real implications for prevention through lifestyle changes. This information does, however, have substantial implications for prevention by pharmacological methods when these are indicated. Aspirin and thrombolytic therapy are now central to the management of suspected infarction through their effects on platelets and fibrin deposition, respectively, and aspirin is indicated in long-term secondary prevention as well. An interesting and so far unresolved puzzle is why aspirin in primary prevention seems mainly to reduce the incidence of non-fatal rather than fatal episodes, although this previously fairly clear distinction has probably become less so with the results of the recently published Italian trial showing a large reduction in cardiovascular deaths, most of which were presumably from fatal CHD. Overall, taking account of the bleeding risk associated with aspirin, its use in primary prevention should be confined to those at particularly high risk—for example, where there is a strong family history of premature CHD. After a considerable vogue for its use and then many years in the wilderness because of emotive criticisms by senior physicians in the late 1960s and the 1970s, warfarin is once
again being considered for its clear value in the secondary prevention of CHD. Much of the increasing interest in its use depends, however, on its particularly obvious effect in reducing thromboembolic stroke in patients with atrial fibrillation. In addition, several studies have shown that warfarin may, in some settings, be just as effective in preventing venous thrombosis at lower intensities of anticoagulation than those previously considered necessary, with a concomitant reduction in the risk of serious bleeding.\textsuperscript{20,21} Turning to CHD, low intensity oral anticoagulation with warfarin has been assessed in one primary prevention trial\textsuperscript{22} where it led to a 39\% reduction in fatal events but to only a small and statistically non-significant effect on fatal episodes. At the intended level of anticoagulation (an international normalized ratio [INR] of about 1.5), it led to no more serious bleeding than 75 mg aspirin. So an important research question now is to confirm or refute the possibility that warfarin does have a large effect on fatal events since it is still difficult, and in a clinical setting virtually impossible, to predict whether a first episode of CHD will be fatal or not and in view of the perhaps limited effect of aspirin on fatal events in primary prevention. There is recent and particularly thought-provoking evidence that warfarin may exert its effect through a long-term, delayed effect on the vessel wall as well as—or even to a greater extent than—its short-term antithrombotic effect which has always provided the main rationale for giving it. The evidence comes from the Post Coronary Artery Bypass Graft trial\textsuperscript{23} which incorporated low-intensity warfarin to an INR of about 1.4 with the maximum dose of warfarin capped at only 4 mg, along with two intensities of lipid-modifying treatment in a factorial design. Warfarin had little or no effect during the 4-year period of the trial itself and while patients were on treatment so at an INR of 1.4 it was not exerting an antithrombotic effect. However, after the treatment phase a clear and significant benefit due to warfarin has emerged. These observations might be explained by a level of anticoagulation that may not affect thrombogenic potential significantly in those with CHD while nevertheless having a worthwhile long-term effect on the vessel wall. The possible effect of warfarin on vessel wall pathology as well as on thrombogenesis and the increasing evidence that thrombin is involved in both processes may be part of a most welcome resolution of the debate between those who have so far tended to concentrate on one or the other. Another way in which these two hypotheses, might be reconciled would be trials of the simultaneous use of lipid-modifying and antithrombotic regimens of which, surprisingly, probably only one has so far been started. The value of modifying fibrin deposition through thrombolytic therapy has already been demonstrated in the absence of oral agents that obviously improve fibrinolytic activity where this is indicated, avoiding overweight and dealing with obesity may be the most promising approaches since they—along with other features of the insulin resistance syndrome—appear to be major determinants of impaired activity. The glycoprotein-I\textsubscript{IB}-III\textsubscript{a} inhibitors of platelet aggregation may be of value in the acute management of myocardial infarction but have not so far been shown to be effective in the longer term setting of primary prevention.

So the wheel seems to have come full circle—thrombosis has rejoined the lipid hypothesis in jointly explaining the sequence of events leading from the pathology to the clinical expression of CHD. At all events, the last two decades or so have fortunately seen investigation of the thrombotic component of CHD advancing rapidly at all levels—in the laboratory, clinically, epidemiologically and through randomized controlled trials. Not many of those who have been engaged in this work or Morris himself probably realize even now just how much this progress in fact owes to his early population-based studies of its pathology.

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