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Review

Plaque fissuring—the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina

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The clinical management of acute myocardial infarction and crescendo angina as well as the prevention of sudden ischaemic death require accurate knowledge of the underlying arterial pathology. It is on just this aspect that until recently there has been disagreement particularly among pathologists. In brief, this controversy was concerned with whether coronary artery thrombi were or were not directly responsible for all three clinical pictures of acute ischaemia.

Resolution of the controversy has been derived from coronary angiography in life in patients with acute infarction and crescendo angina and from detailed pathological studies. These latter studies differ from many carried out previously by the use of postmortem coronary angiography and histological reconstruction of the microanatomy of occlusive lesions.

Findings in life

Clinical angiography has shown that the incidence of occlusion in the coronary artery supplying a myocardial infarct is very high during the early period after the onset of symptoms. Figures of around 90% are consistently reported within an hour of the appearance of electrocardiographic changes of infarction, but the incidence of acute occlusions thereafter falls to around 50% at 12–24 hours.[1 2] The implication is that blood flow has been restored by natural processes which, judged by their rapidity, can only be by lysis of thrombus or relaxation of spasm or a combination of the two. A number of clinical angiographic appearances—including persistent retention of contrast medium by intraluminal material, an irregular or lobulated margin to the occlusion, and filling defects within the lumen—have been taken to indicate a thrombotic occlusion.[3] In postmortem coronary arteriograms areas of stenosis with ragged margins and intraluminal transluscency have been shown to be a reliable indicator of the presence of thrombus.[4] The success of either intracoronary streptokinase infusion or systemic streptokinase-plasminogen activator in restoring arterial patency strongly suggests that thrombus is a major element in the occlusion. Flow can be restored in 72–96% of such cases[3 5–8] using intracoronary infusion and in 45–65% of cases using intravenous infusion of fibrinolysins.[9] Fibrinolytic agents that specifically bind to recent thrombus[10] may well improve the latter rate. As the arterial flow is restored by fibrinolysis a sequence of angiographic appearances develops which includes all those taken to indicate the presence of thrombosis.[3 11–13] Such appearances, in particular intraluminal filling defects, would be most unlikely to occur if the occlusion had been due purely to spasm of an atheromatous artery.

After fibrinolysis, in most cases but not all, a high grade stenotic lesion is usually found in the artery supplying the area of infarction.[6 7 14 15] After fibrinolysis thrombosis recurs in up to 25% of cases,[6–8 11 12] particularly in those with the higher grades of residual stenosis.[16]

In crescendo angina, the causative role of thrombus is less firmly based, but angiographic appearances suggesting non-occlusive (mural) thrombus to be present have been found in 85% of cases[17–19] or even in all cases.[20] In cases where an acute infarct has developed complete arterial occlusion has been found.[11 19] The beneficial effect of aspirin treatment in reducing the risk of sudden death and acute infarction in cases of crescendo angina also points to an

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underlying thrombotic process.[21]

Thus there are compelling reasons to believe that thrombus plays a major role in both acute myocardial infarction and in crescendo angina. What has been added by these clinical studies is the evidence that thrombosis is a rapidly changing dynamic process reflecting equally rapid changes in the arterial lesion.

Necropsy findings

Recent pathological studies, in which the coronary thrombi found in fatal cases of acute myocardial infarction were reconstructed from serial histological sections, have shown that virtually all were related to rupture or fissuring of atheromatous plaques.[22 23] Rupture of a plaque leads to free communication between the lipid content of the plaque and the blood flowing within the arterial lumen. Dissection by blood from the lumen into the plaque, in many cases, results in a large intraintimal thrombus rich in platelets. Over the site of rupture thrombus develops within the lumen and often propagates distally into segments of the artery without significant intimal disease. Such studies emphasise that the head of the thrombus in relation to the plaque is different from the thrombus propagating distally[24]; the former is rich in platelets, the latter contains a higher proportion of fibrin. These postmortem studies have usually been carried out in cases where a large regional infarct is found at necropsy and the coronary artery is totally occluded, the patient having lived for at least 24 hours after the onset of symptoms.

Study of patients who die suddenly of ischaemic heart disease[25] shows that 95% of such cases have an acute evolving coronary arterial lesion. These lesions are also atheromatous plaques undergoing fissuring or rupture. All the clinical angiographic appearances regarded as indicating thrombosis are present also in postmortem angiograms in sudden ischaemic death (Figs. 1 and 2). Histological examination confirmed that in 74% of cases there was recent thrombus present in the lumen, but this did not necessarily totally occlude the vessel. In a further 21% there were plaque fissures with recent thrombi within the intima but not in the lumen. Compared with that in patients dying in hospital with established myocardial infarction the

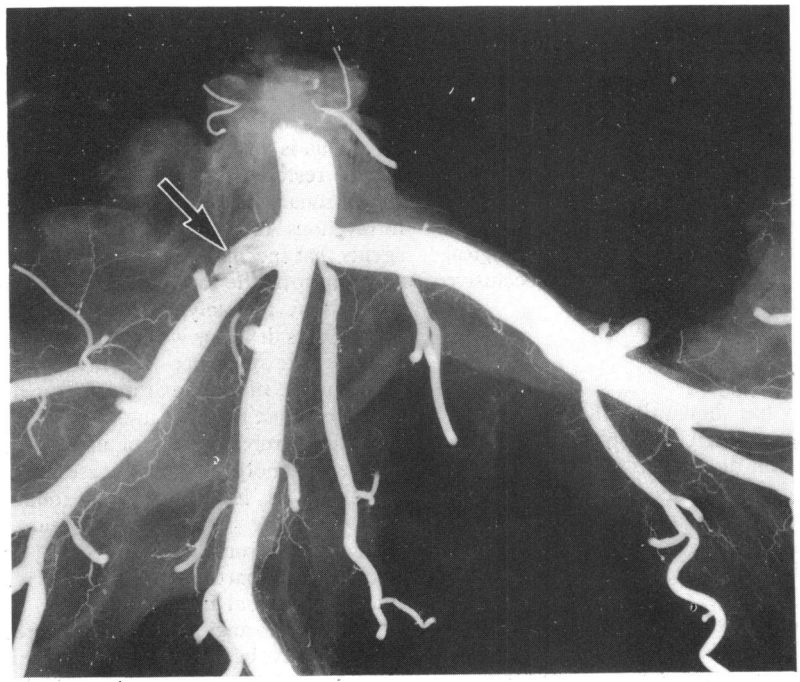

Fig. 1 *Postmortem angiogram of a man aged 44, who had no previous history of angina and was extremely fit. During a game of squash he suddenly felt unwell with chest pain and died 30 minutes later. The left anterior descending artery divided into two major branches immediately after the origin. One of these showed an intraluminal filling defect (arrow) associated with an irregular intimal outline. Histology confirmed a fissure of a plaque with overlying thrombus. The remainder of the coronary artery tree was angiographically and histologically normal.*

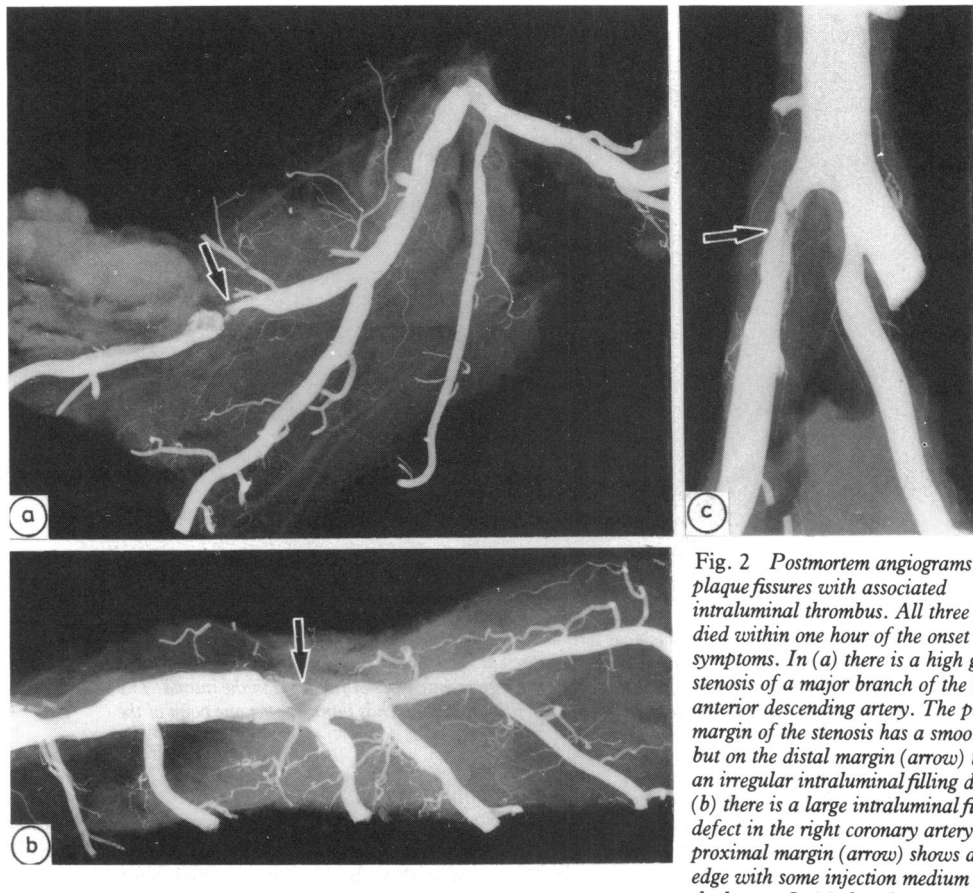

Fig. 2 *Postmortem angiograms showing plaque fissures with associated intraluminal thrombus. All three patients died within one hour of the onset of symptoms. In (a) there is a high grade stenosis of a major branch of the left anterior descending artery. The proximal margin of the stenosis has a smooth edge, but on the distal margin (arrow) there is an irregular intraluminal filling defect. In (b) there is a large intraluminal filling defect in the right coronary artery. The proximal margin (arrow) shows a straight edge with some injection medium outside the lumen. In (c) there is a translucent (arrow) line projecting into the lumen with a small linear intraluminal filling defect. In all three cases good distal filling of the vessel was present.*

incidence of a totally occlusive thrombus with distal propagation is low in sudden ischaemic death. Thus the lesions in the coronary arteries in cases of sudden ischaemic death are essentially the same as those found in cases of acute infarction but have a lesser degree of intraluminal thrombus formation.

Events in a dynamic process

Taking these clinical and pathological findings together a probable sequence of events can now be proposed. Atheromatous plaques, as seen in arteries distended and fixed at physiological pressures, bulge outward toward the media[26 27] (Fig. 3). In lipid rich plaques there is a crescentic mass of cholesterol and its esters, the lipid pool, separated from the lumen by fibrous tissue. This fibrous cap is often thinnest over the points of the crescentic shaped plaque. Rupture of the fibrous cap (Figs. 4–6) allows dissection into the intima by blood from the lumen into the lipid pool of the plaque. A mass of thrombus rich in platelets, but also containing some red cells and fibrin, forms within the intima and leads to considerable expansion of the plaque. Over the site of rupture, thrombus forms in the lumen but this mass of luminal thrombus initially does not occlude the lumen but waxes and wanes in size over hours or even days. The amount of thrombus forming within the lumen is not always directly proportional to the magnitude of the exposure of lipid in the plaque. Some patients (Fig. 7) may have a massive thrombotic response within the lumen with minimal fissuring. Ultimately, the intraluminal thrombus may grow to become totally occlusive or be completely lysed and the plaque fissure reseal, stabilising

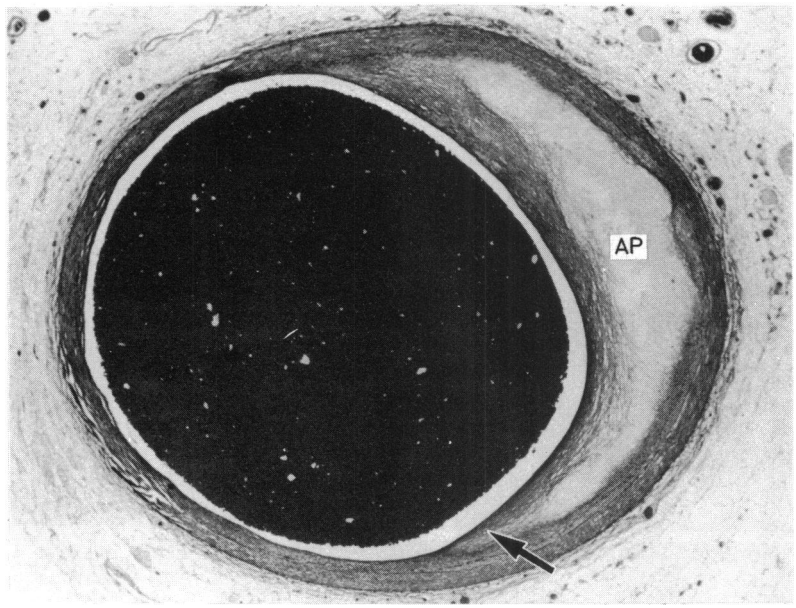

Fig. 3 *Transverse histological section of a coronary artery perfused and fixed at 100 mm Hg. No significant stensosis is present. The lumen contains angiographic medium and is round in outline. The plaque (AP) is a crescentic mass of free lipid in the intima. The lipid pool is separated from the lumen by a fibrous cap which is thinnest over one point of the crescent (arrow).*

the atheromatous plaque, albeit now considerably larger than before. By these processes patients with crescendo angina or those who suffer sudden ischaemic death have coronary artery lesions in the earlier stages of plaque fissuring. Patients who develop an established regional infarction are those in whom the thrombus had occluded the lumen at least for long enough to induce myocardial necrosis (Figs. 8 and 9). Experimental evidence suggests that this may need to be only 18 minutes of total occlusion.[28]

The basic arterial pathology of sudden ischaemic death and acute myocardial infarction is thus identical, only differing in being at different stages of the same process. The question is now posed as to why some patients should suddenly die of ventricular fibrillation before the arterial lesion is fully occlusive. Here the pathologist can give no firm answer but only hypothesise. In a small proportion of cases dissection from the lumen into the intima raises a tissue flap giving a degree of mechanical obstruction. In a larger proportion of cases the plaque has been suddenly increased in volume by thrombosis within the intima and in such circumstances the plaque encroaches on the lumen to the extent of suddenly increasing the degree of obstruction. When thrombus develops within the lumen it is a potential source of platelet emboli into small vessels in the myocardium. Some investigators have reported a high incidence of platelet emboli within the myocardium at necropsy in cases of sudden ischaemic death.[29 30] Sudden death may thus be the myocardial equivalent of transient cerebral ischaemic attacks due to platelet emboli arising from fissured and ulcerated atheromatous plaques in the carotid arteries. Finally, tearing of the intima and consequent deposition of thrombus could invoke local arterial spasm. An element of spasm in the total occlusions causing myocardial infarction has been reported[31] but is probably rare.[12] It seems certain that many patients do survive plaque fissuring without developing any clinical symptoms, and myocardial susceptibility to ventricular fibrillation must be an important and additional factor in precipatating sudden ischaemic death in certain individuals.

By this concept of the vascular pathology the three acute cardiac ischaemic presentations have a common basis (Fig. 9). Patients with a plaque fissure but who escape the three acute clinical expressions will be left with atheromatous plaques far larger than previously, and such episodic plaque growth[32] is an important factor in the developement of stable angina.

Previous contradictions explained

If the proposed mechanisms are true then much in the past that has apparently been contradictory can be

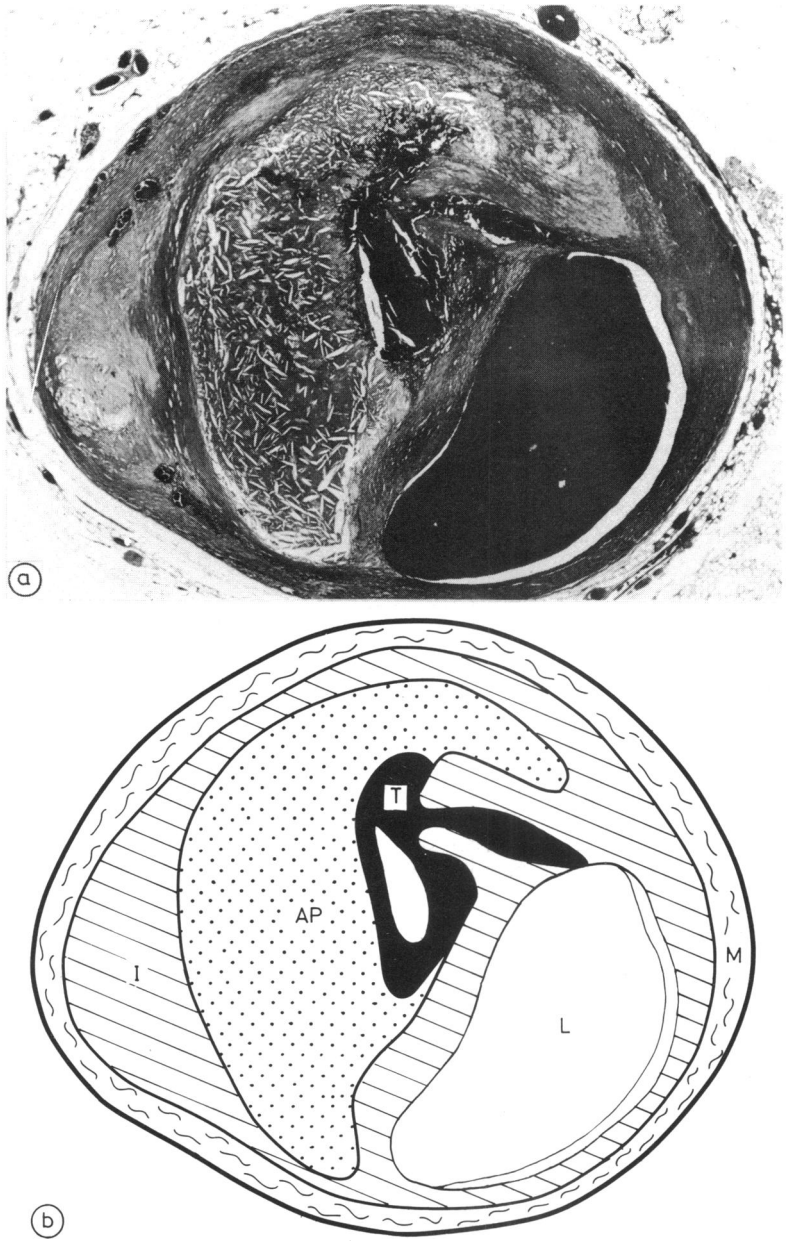

Fig. 4 *Transverse histological section of a fissured plaque (AP) (a) with accompanying diagram (b). Angiographic medium is present in the lumen (L); despite the vessel having been perfuse-fixed the plaque bulges into the lumen. A fissure extends from the lumen into the plaque, which contains a mixture of angiographic medium and thrombus (T). No intraluminal thrombus is present at this point. I, intima; M, media.*

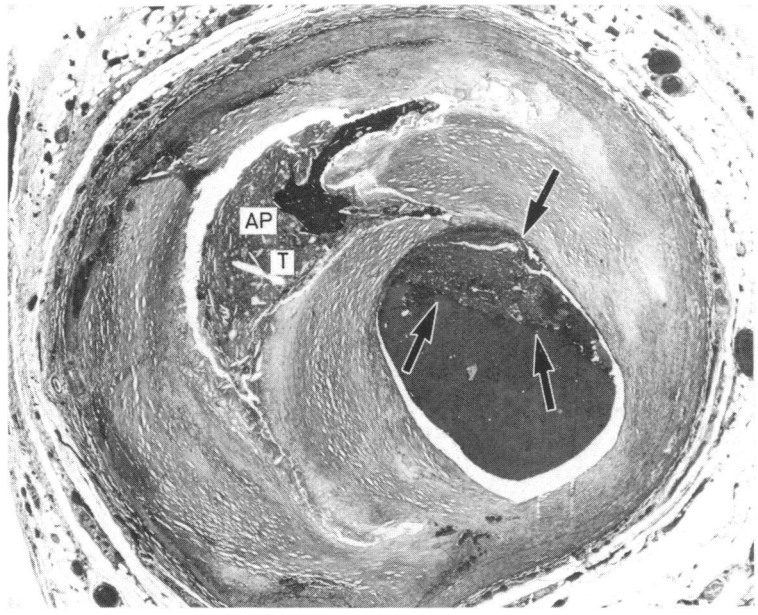

Fig. 5 *An adjacent distal histological section shows the plaque (AP) is smaller at this point but still contains injection media and thrombus (T). Mural thrombus (arrows) is present projecting into the lumen and attached at the intima close to the fissure site.*

explained. If thrombi evolve and regress over a relatively short period of time a pathologist carrying out a necropsy cannot have a precise picture of the state of the coronary arteries some days earlier when the patient first developed chest pain. Those pathological series reporting a high incidence of coronary thrombi[33-36] are biased towards patients with large regional infarcts dying in hospital. It is just such cases that have major plaque fissures with persistent total occlusion and inexorable distal propagation of thrombus. Series that report a lower incidence of thrombosis[37-40] probably contain a higher proportion of cases with smaller infarcts or even sudden death, in which the associated plaque fissure was less major and intraluminal thrombus smaller. These smaller thrombi may have spontaneously lysed before death or not been discovered at necropsy.

The acute arterial lesions associated with sudden ischaemic death are smaller than those of regional infarction and require more technical expertise for their demonstration. As there is usually no infarct recognisable at this stage the pathologist is not focused to examine a particular artery. Few of the reported studies of sudden ischaemic death have used techniques that would demonstrate the arterial pathology with certainty. Postmortem arteriography is almost certainly necessary unless the pathologist is unusually meticulous. Larger, more easily detected, thrombi are likely to be present in patients who have lived longest from the onset of symptoms, and this is the explanation of the often quoted work of Spain and Bradess,[41] who found the incidence of coronary thrombi to rise with the time interval between the onset of pain and death. A study of sudden ischaemic death in which postmortem angiography was used found thrombi in a high proportion of cases with no relation to the time interval.[25]

Once it is accepted that distal propagation of thrombosis occurs from a proximal nidus the discordant reported results of radiolabelled fibrinogen studies are easily explicable. Erhardt *et al* gave radiolabelled fibrinogen to patients with acute infarction as soon as possible after the onset of pain.[42,43] In those who died radiolabel was found at necropsy in the thrombus. These results led to the hypothesis that thrombus was secondary to and not the cause of infarction. This view was effectively quashed by Davies *et al* and Fulton and Sumner,[24,44] who by similar techniques showed the head of the thrombus over the plaque to be radionegative, the distal tail only being positive. This work is entirely in accord with the current pathological concept being propounded.

Clinical studies of patients resuscitated from apparent sudden death show that only a proportion developed acute myocardial infarction,[45,46] which has

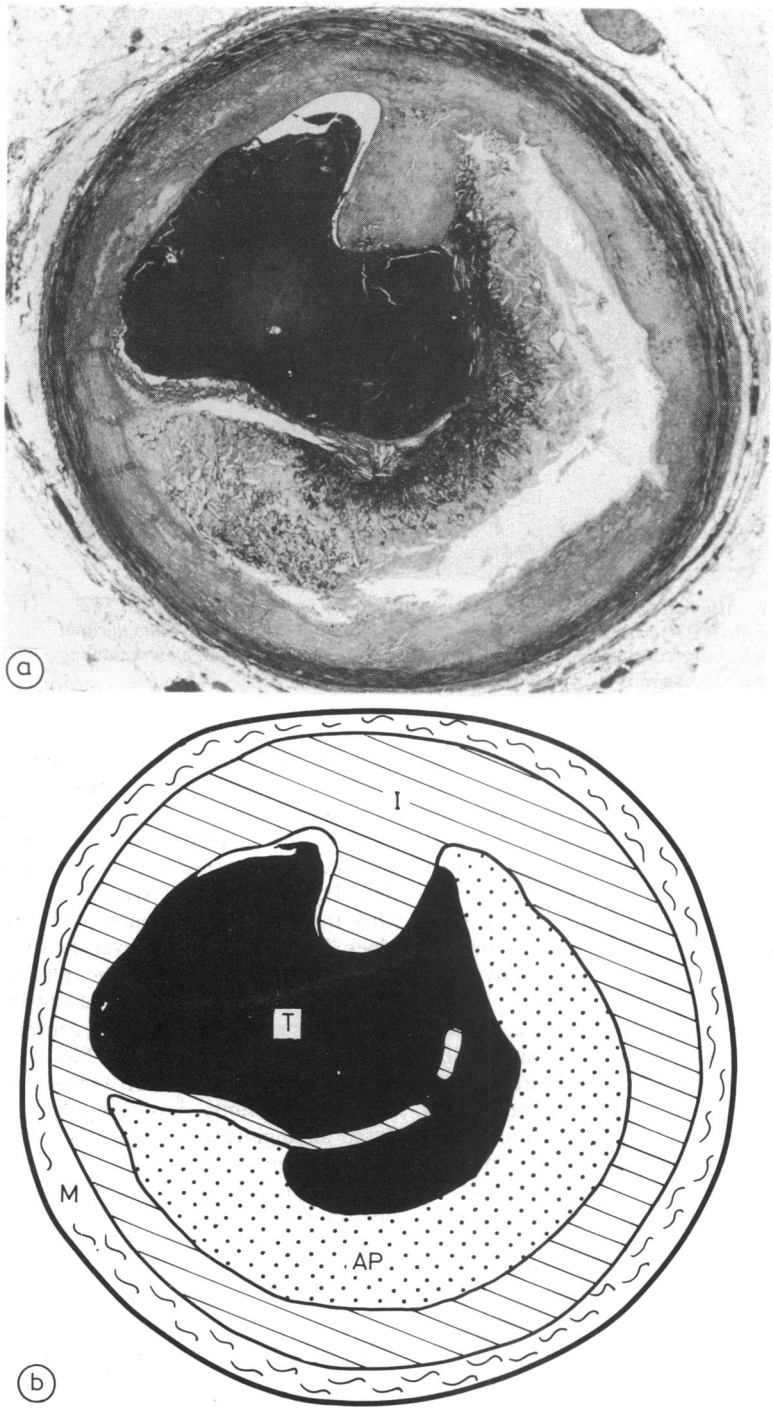

Fig. 6 *Histological cross section of a major plaque rupture (a) and accompanying diagram (b). The plaque (AP) has a large defect in the fibrous cap, through which a dumb bell mass of thrombus has formed, part being within the plaque and part virtually occluding the lumen.*

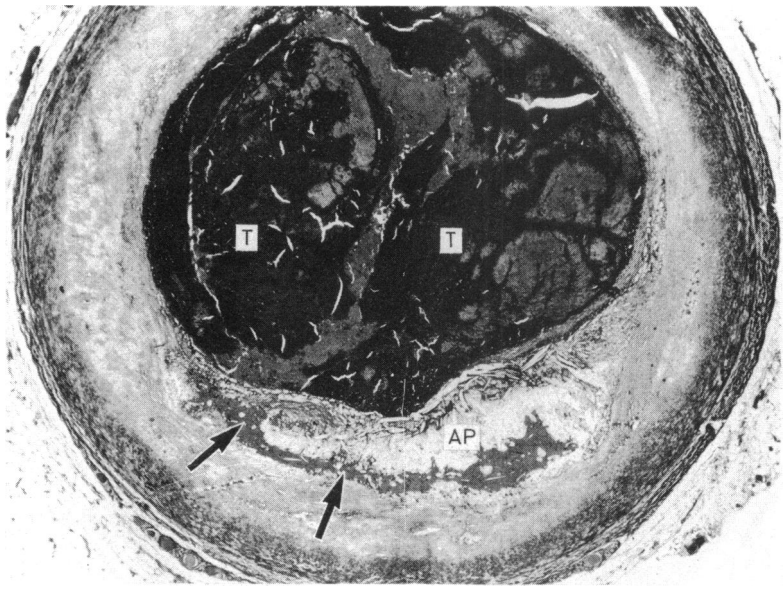

Fig. 7 *Minimal plaque fissuring associated with massive intraluminal thrombus. The plaque itself (AP) was very small, but injection media (arrow) passed easily into the lipid pool, which also contains thrombus. The lumen is occupied by a large mass of dark staining thrombus (T), which is mixed with injection media.*

been interpreted as indicating that "sudden ischaemic death" is bimodal—a group with coronary thrombosis and a group without. This view is probably an oversimplification, and it is more likely that every individual had a plaque undergoing fissuring but only a subset developed an intraluminal thrombus which was totally occlusive for long enough in time to cause infarction. In the remainder the intraluminal thrombus was not of this magnitude and subsequently lysed allowing the plaque to restabilise.

If it is accepted that plaque fissuring is a random event in lipid rich plaques there are some clinical corollaries. A proportion of patients with infarction or pending sudden death have been unfortunate enough to develop fissuring in one of the few plaques they possess. Their prognosis, if they survive, may be excellent without a further episode for many years. In contrast a patient with numerous plaques has a higher risk of repeated episodes.

Those plaques which do undergo rupture usually have a large lipid rich pool. It is often assumed that these will cause sufficient stenosis to be recognised at clinical angiography. Study of the relation of the previous degree of stenosis to thrombosis suggests that thrombosis tends to occur on plaques where the lumen has already been reduced by more than 50% by diameter.[40] It is, however, very difficult to measure accurately the previous stenosis caused by a plaque that has extensively fissured. Data on the degree of stenosis present in clinical angiograms after treatment of coronary thrombosis by fibrinolysis do not contribute since the plaques in question will have been enlarged by a sequestered acute intraintimal thrombus. It is far from clear what effect lysis has, if any, on this intraintimal component. The residual stenosis does, however, decrease over days or weeks suggesting that remodelling of the plaque must occur.[7] Pathological studies of cases of sudden death,[25] however, do suggest that fissuring can develop in plaques which are causing less than 50% stenosis by diameter. If such individuals develop a minor fissure over which a large thrombus develops which is subsequently lysed an angiographic appearance results which may be interpreted as normal. This process probably explains an unknown proportion of patients in whom infarction occurs with apparently normal arteries and is an alternative explanation to spasm as the causative factor.[47–49]

Process of plaque fissuring

Plaque fissuring is not a recent dicovery; its importance, however, is only now being fully appreciated. Throughout the last 60 years there has been considerable interest in the acute changes in plaques that initiate thrombosis. In 1926, Benson found that thrombi in the coronary arteries arose on

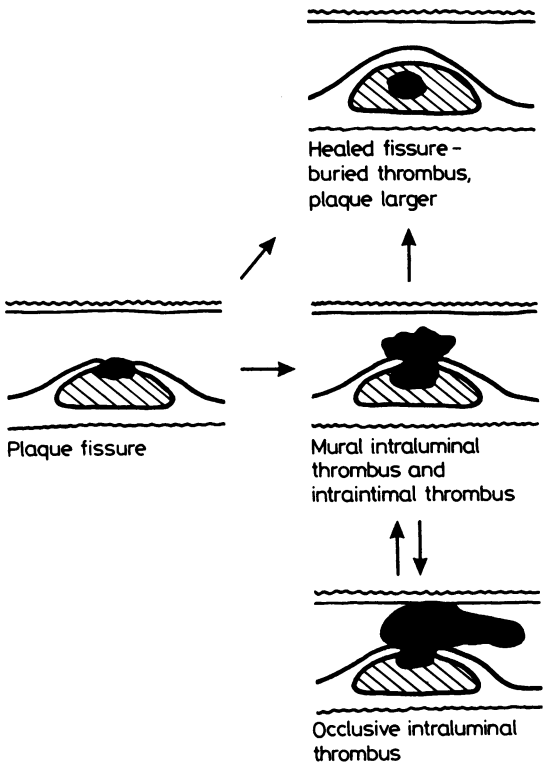

Fig. 8 *Diagrammatic representation of the evolution of a plaque fissure either to reseal and stabilise or to progress to thrombotic occlusion.*

the intima overlying plaques which had physically broken allowing, in his words, "dissecting haemorrhage from the lumen into the plaque."[50] Since that time many others have confirmed these lesions describing them as tears, breaks, ulcers, or ruptures of atheromatous plaques.[51 52] An early study of 32 coronary thrombi associated with myocardial infarction showed all to be related to "ulceration" of the plaque.[53] There was thus established the view that coronary thrombosis followed major physical disruption of the intima exposing lipid to the flowing blood. By disruption was meant gaps many micrometres or even millimetres in size demonstrable by conventional microscopy.

The basic principle was subsequently, and regrettably, undermined. Paterson described free red cells to be present within atheromatous plaques and ascribed this "haemorrhage" to bleeding from small vessels entering the intima from the media.[54 55] Paterson concluded that plaque haemorrhage was common and usually unassociated with overlying thrombosis. Argument raged over whether bleeding from such transmedial vessels could cause plaque growth sufficient to occlude the lumen but, in general, it was thought that intraluminal pressure would limit the bleeding. To many authorities in the field,[56] the work of Constantinides had finally re-established the importance of fissures from the lumen.[57] In 17 thrombi causing acute myocardial infarction reconstructed from serial sections cracks or fissures were found and "haemorrhage" in the plaque could be traced to an entry into the plaque from the lumen.[57] A view persisted, however, in the minds of some that fissures were "artefacts." This scepticism may be related to the ascendancy of the postulates of Duguid, who stated that fibrin within a plaque represented earlier surface thrombus incorporated into the intima.[58] This view of the growth of atheromatous plaques would be seriously weakened if it were to be accepted that intraplaque thrombus formation occurs via a fissure from the surface into the core of the plaque.

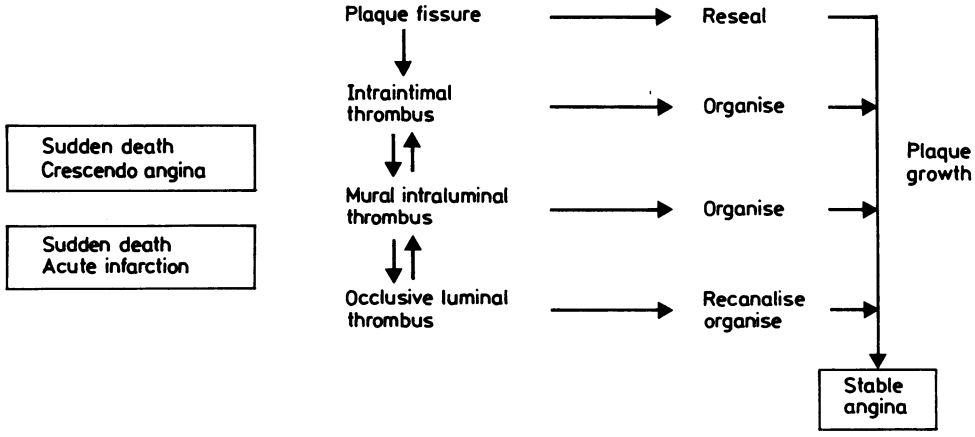

Fig. 9 *Relation between the clinical expressions of ischaemic heart disease and the stages of plaque fissuring.*

Conclusions

It can now be appreciated that there are two quite different processes encompassed by the term "plaque haemorrhage." The fact that the media behind plaques becomes intensely vascularised and that these vessels enter the intima is beyond dispute.[59 60] Bleeding from such vessels crossing the media causes a limited number of red cells to lie free within the lipid pool of many plaques. No fibrin or platelets are present, and the process is almost ubiquitous in large lipid rich plaques. The second process is the presence of large numbers of red cells, masses of platelets, and considerable amounts of fibrin within the plaque. If serial histological sections are used these elements can be traced to an entry into the lumen via a fissure, although this may be closed by a mass of thrombus. The two processes must be clearly separated and the term intraplaque thrombosis is more applicable to that associated with fissures from the lumen. It is plaque fissuring with related intraintimal thrombosis progressing to the formation of an intraluminal thrombus that is the important dynamic process unifying crescendo angina, acute myocardial infarction, and sudden ischaemic death.

It is difficult to escape the conclusion that the failure of pathologists to think in terms of dynamic processes and to believe what was seen at necropsy was an immutable reflection of events in life that occurred days before has seriously hindered the understanding by clinicians of how atheroma produces acute clinical symptoms.

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