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Coronary Arteries in Fatal Acute Myocardial Infarction

By WILLIAM C. ROBERTS, M.D.

SUMMARY

The coronary arteries are diffusely involved by atherosclerotic plaques in fatal acute myocardial infarction (AMI). The degree of luminal narrowing may vary but plaques are present in practically every millimeter of extramural coronary artery. Usually the lumens of at least two of the three major coronary arteries are narrowed >75% by old plaques in patients who die suddenly (<6 hours) from cardiac disease with or without myocardial necrosis. Coronary thrombi occur in about 10% of patients who die suddenly or in whom necrosis is limited to the left ventricular subendocardium, and in about 50% of patients with transmural myocardial necrosis. Coronary thrombi usually indicate the presence of shock or congestive heart failure or both during the development of myocardial necrosis. The infrequency of coronary thrombi in patients dying suddenly of cardiac disease and in those with transmural necrosis who never have shock or congestive heart failure suggests that the thrombi may be consequences rather than causes of AMI.

Although it may not precipitate AMI, coronary thrombosis may still be the underlying cause of the atherosclerosis. The finding of fibrin deposits in old atherosclerotic plaques and the findings of atherosclerotic-type lesions (cholesterol clefts, foam cells, pultaceous debris, calcific deposits) in organized known thrombi (as in the left atrium in mitral stenosis) suggest a strong relationship between thrombosis and atherosclerosis.

Coronary arterial emboli are not rare; they are located in distal portions of the coronary tree and are present in the small epicardial branches as well as in intramural coronary arteries. In contrast, coronary thrombi are located in proximal portions of major extramural vessels, are infrequent in the small epicardial branches, and are absent in intramural coronary arteries. Coronary atherosclerosis is limited to the extramural coronary arteries and spares the intramural coronary arteries.

Additional Indexing Words:

Atherosclerosis Coronary thrombosis Coronary hemorrhages Shock
Congestive cardiac failure Coronary embolism Intramural coronary arteries

THIS PAPER focuses attention on the coronary arteries in fatal acute myocardial infarction (AMI) and attempts to present evidence that the following conclusions about this condition are valid: (1) that the extramural coronary arteries are diffusely involved by old atherosclerotic plaques; (2) that thrombi in extramural coronary arteries are infrequent in patients dying suddenly and in those with only subendocardial necrosis; (3) that thrombi, when found in extramural coronary arteries in transmural infarction, generally indicate the presence of pump failure for some time before death; (4) that thrombi in coronary arteries usually are located at, and just proximal to, sites already severely narrowed by old atherosclerotic plaques; (5) that although coronary arterial thrombi do not appear to precipitate AMI, thrombosis, nevertheless, may cause the underlying atherosclerosis; (6) that coronary atherosclerosis does not involve intramural coronary arteries; and (7) that coronary arterial emboli are not rare and that their pathology is usually distinctive.

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Diffuse Nature of Extramural Coronary Arterial Atherosclerosis in Fatal AMI

The extramural coronary arteries are diffusely involved by old atherosclerotic plaques in patients dying of AMI[1] (figs. 1 and 2). The degree of luminal narrowing varies, but some plaques are present on the intimal surface of virtually every millimeter of major artery. The extent of the coronary arterial atherosclerotic process in fatal AMI was dramatically demonstrated to Roberts and Buja by examination of three histologic sections in every 5-mm segment of the entire left main, left anterior descending, left circumflex, and right coronary arteries.[1] Of several thousand histologic sections of coronary arteries examined in 74 patients with transmural necrosis, in nine patients with subendocardial necrosis and in 24 patients who died suddenly (<6 hours after onset of symptoms, but with no myocardial necrosis), only four sections (excluding those in three patients with coronary arterial emboli) were free of old atherosclerotic plaques. A coronary artery, however, may contain a considerable amount of atherosclerosis and yet be capable of transporting substantial quantities of blood to the myocardium. When the degree of coronary narrowing decreases the original lumen by more than 75%, the flow in the vessel is significantly decreased. In the carotid artery, a detectable reduction in flow and pressure does not occur until the degree of luminal narrowing is >80%.[2] Among the 107 necropsy patients studied by Roberts and Buja, the average number of major coronary arteries (three per patient, excluding the left main) narrowed >75% by old atherosclerotic plaques were: 2.4 in 74 patients with transmural necrosis; 2.1 in nine patients with only subendocardial necrosis; and 2.4 in 24 patients who died suddenly. Similar observations had been made by Saphir and associates,[3] Blumgart et al.[4] and Yater et al.[5] who found "complete occlusions" of usually two major coronary arteries in patients dying with angina pectoris or of AMI. The degree of coronary arterial luminal narrowing by old atherosclerotic plaques is identical in patients with fatal AMI who have coronary thrombi and in those without coronary thrombi.[6]

The sites of maximal narrowing of major extramural coronary arteries are highly variable from patient to patient, but certain patterns emerge when large groups of patients with fatal AMI are examined. The lumen of the left main coronary artery is infrequently narrowed >75% by old atherosclerotic plaques. In two of the 107 patients studied by Roberts and Buja this vessel was narrowed to this degree. Maximal narrowing of the left anterior descending and left circumflex coronary arteries is usually within 2 cm of the bifurcation of the left main artery. The proximal and midportions of the right coronary artery also appear to be predisposed to greater degrees of luminal narrowing by old plaques than does the distal portion. The main function of the right coronary artery is to supply the posterior wall of left ventricle via its posterior descending branches. Thus, narrowing of the right coronary artery at any site proximal to the origins of the posterior descending branches might have similar functional significance. In other words, the left coronary arterial tree begins supplying the left ventricle with oxygen about 2 cm from its origin from the aorta; the right coronary artery does not begin perfusing the left ventricle until it has traveled in the right atrioventricular sulcus for about 12 cm. Thus, severe narrowing of the right coronary artery 11 cm from its aortic ostium might be as significant a lesion as a similar narrowing 2 cm from its ostium. In contrast, severe narrowing of the left anterior descending coronary artery 11 cm downstream without significant proximal narrowing may have minor myocardial consequences.

Atherosclerotic lesions generally have been classified into three types:[7] (1) yellow (fatty) streaks or dots; (2) fibrous plaques; and (3) complicated plaques. The latter plaques contain calcific deposits, cholesterol clefts, thrombus, or all three, and they may ulcerate (into the arterial lumen) or weaken the vessel wall so that it dilates. The atherosclerotic plaques

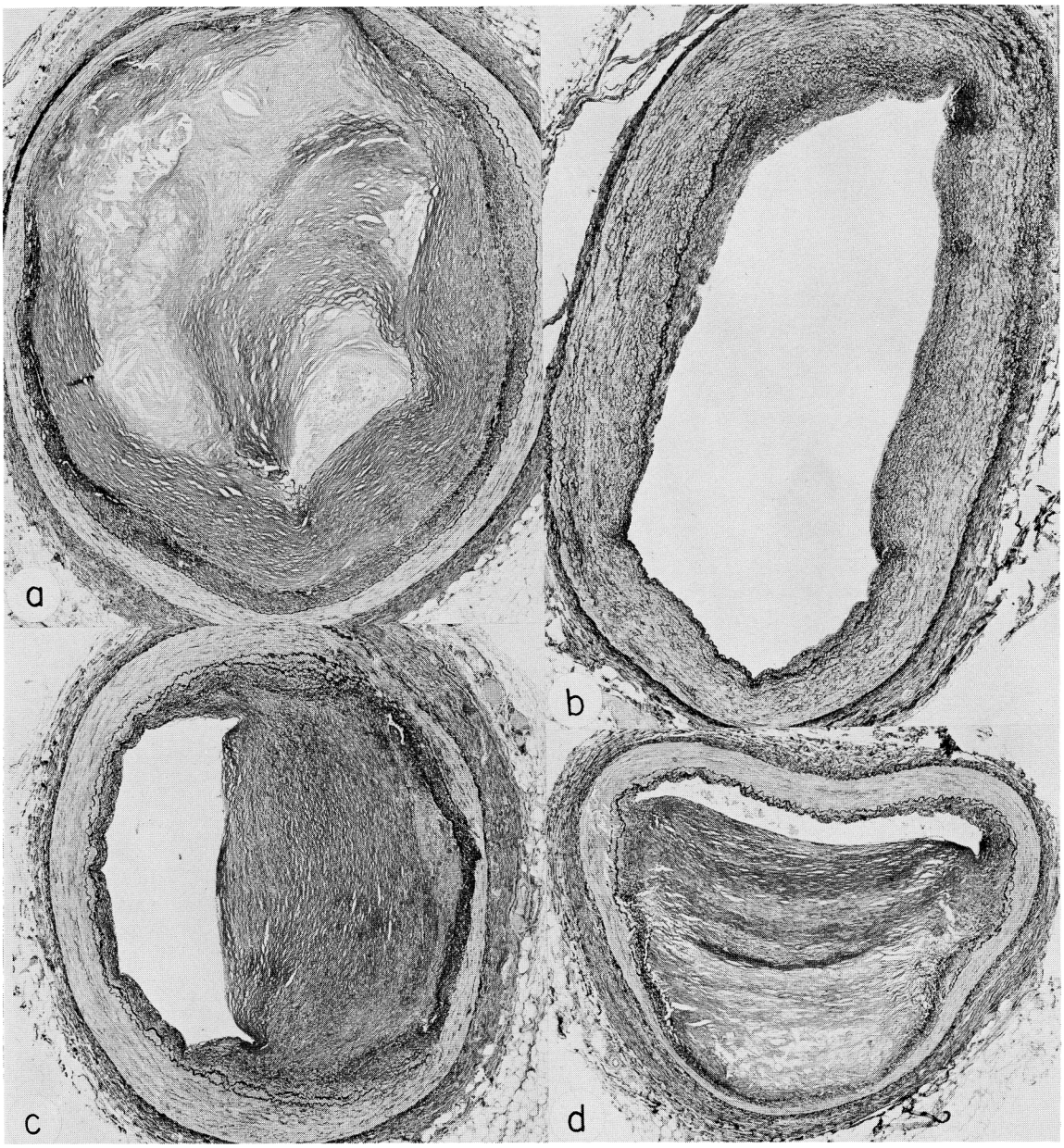

Figure 1

Major extramural coronary arteries at site of maximal narrowing in a 54-year-old woman (SH#A4571) who died suddenly at home. She had had angina pectoris for several years but never a myocardial infarct or congestive cardiac failure. At autopsy, the heart weighed 300 g, and no foci of myocardial necrosis or fibrosis were present. (a) *Right coronary artery 3 cm from the aortic ostium. The lumen is >90% obliterated.* (b) *Left main artery.* (c) *Left circumflex artery in the first 1 cm.* (d) *Left anterior descending artery 3 cm from the bifurcation of the left main artery. The luminal narrowing in each vessel is due entirely to old plaques. No thrombi or hemorrhages into plaques were found. (Elastic van Gieson stains, each × 31.)*

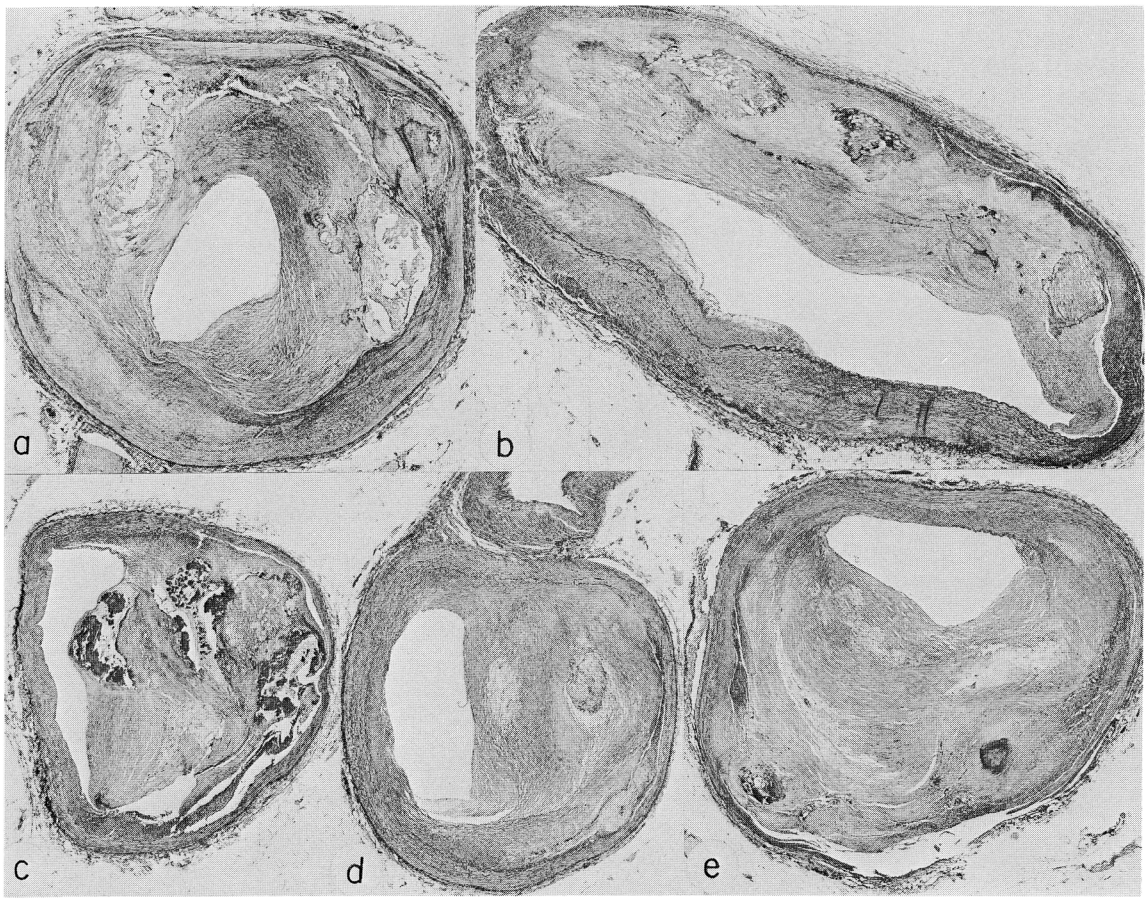

Figure 2

Major coronary arteries at sites of maximal narrowing in a 71-year-old man (SH#A4489) who died suddenly of left ventricular free-wall rupture 9 days after onset of acute myocardial infarction. At no time during his life was congestive cardiac failure or shock noted. At autopsy, the heart weighed 390 g, and no thrombi or hemorrhages were observed in the coronary arteries. (a) *Right artery.* (b) *Left main artery.* (c) *Left marginal artery.* (d) *Left circumflex artery. (e) Left anterior descending artery. The major arteries (excluding left main and left marginal) were narrowed >75% by old plaques. (Movat stains, each × 20.)*

observed in extramural coronary arteries in fatal AMI are of the complicated type. Significant degrees of coronary arterial luminal narrowing do not result from foam-cell lesions alone, except possibly in patients with type III hyperlipoproteinemia.[8] In most complicated plaques few foam cells are present and the luminal narrowing is caused primarily by fibrous tissue, with or without calcific deposits, and pultaceous debris (presumably the end result of the breakdown of foam cells). Why calcific deposits are absent in coronary arteries of some patients with fatal AMI and extensive in others is unknown. Calcific deposits in these vessels increase with age (>95% of patients in the U.S.A. >80 years of age have coronary arterial calcific deposits[9]), and these deposits are more frequent and extensive in patients with systemic hypertension as compared to normotensive patients.[9] Patients with diabetes mellitus also appear to have larger and more extensive coronary calcific deposits than nondiabetics.

Incidence and Significance of Coronary Arterial Thrombi in Fatal AMI

AMI is generally considered to result from thrombotic occlusion of a major extramural coronary artery. Indeed, *coronary thrombosis* was the name applied originally and used for years to describe AMI both clinically and pathologically. Although many clinicians and pathologists expect to find a thrombus in a coronary artery in fatal AMI, the reported incidence of such thrombosis has varied from 7 to 91%.[1, 3, 10–30] Inclusion of cases of subendocardial infarction and sudden death ("acute cardiovascular collapse in the absence of acute myocardial necrosis")[31] with cases of transmural infarction may be the major cause for the variation in incidence.

Coronary arterial thrombi are infrequent in patients who die suddenly with or without previous histories of cardiac disease and in those with only subendocardial necrosis (limited to the inner one half of the myocardium). Among 24 patients who died suddenly (<6 hours from onset of symptoms) studied by Roberts and Buja[1] two (8%) had a thrombus in a coronary artery; and of nine patients with only subendocardial necrosis, none had coronary arterial thrombus. It contrast, of 74 patients with transmural myocardial necrosis studied in a similar manner by the same authors, 40 (54%) had a thrombus in a coronary artery.

A true thrombus is adherent to the surface of the artery bordering the lumen, and it is composed of platelets or fibrin or both and usually also of erythrocytes and leukocytes. Coronary arterial thrombi are usually about 1 cm in length, and although they are adherent distally they may not be adherent proximally. The composition of a thrombus at varying levels may differ; distally it is likely to consist of platelets or fibrin or both (white thrombus), and more proximally it is likely to be composed of erythrocytes, lesser quantities of fibrin, few platelets, and some leukocytes (red thrombus). Early thrombi may be composed purely of platelets, and they are usually small and nonocclusive.

Thrombi occurring in patients dying of AMI are, except in cases of embolism, superimposed on old atherosclerotic plaques (fig. 3). Usually the artery containing the thrombus is >50% narrowed already by old atherosclerotic plaques and frequently the degree of luminal narrowing is >75% at the distal attachment. In nearly all patients with fatal AMI and coronary arterial thrombi the lumen of the artery distal to the thrombus is >75% narrowed by old plaques. Of 40 patients with coronary arterial thrombi and fatal transmural AMI studied by Roberts and Buja, the artery distal to the thrombus was already >75% narrowed by old atherosclerotic plaques in 36 (90%). In three of the remaining four patients, embolism rather than in situ thrombosis was the cause. Although many investigators have examined by serial sections the coronary arterial segment containing the thrombus, the status of the artery distal to the thrombus has been poorly studied until recently[1] (fig. 3). In a few patients studied by Roberts and Buja the thrombus occurred in a segment of artery between two sites of extreme narrowing by old plaques. Experimentally, the site of predilection of a thrombus has been within such a segment or at the beginning of the poststenotic luminal expansion.[32]

Why fresh thrombi are located at sites of narrowing is unclear. Several investigators[1, 3, 6, 33–40] have observed thrombi covering cracks in old atherosclerotic plaques, and some[36–38, 40] have considered rupture of the innermost layer of plaques the important precipitating cause of coronary arterial thrombosis. Ruptures occur particularly in fibrous tissue covering deposits of pultaceous debris and lead to discharge of necrotic debris into the arterial lumens or to bleeding into plaques. The break in the plaque exposes collagen to the flowing blood, and this site is said to be a strong stimulus for platelet accumulation.[41] The sudden change in volume of the plaque by discharge of plaque material into the lumen or from hemorrhage into the plaque via the rupture also creates alterations in flow patterns which favor platelet thrombosis.[36] Jørgensen[6] has suggested that the pathogenesis of coronary thrombi associated

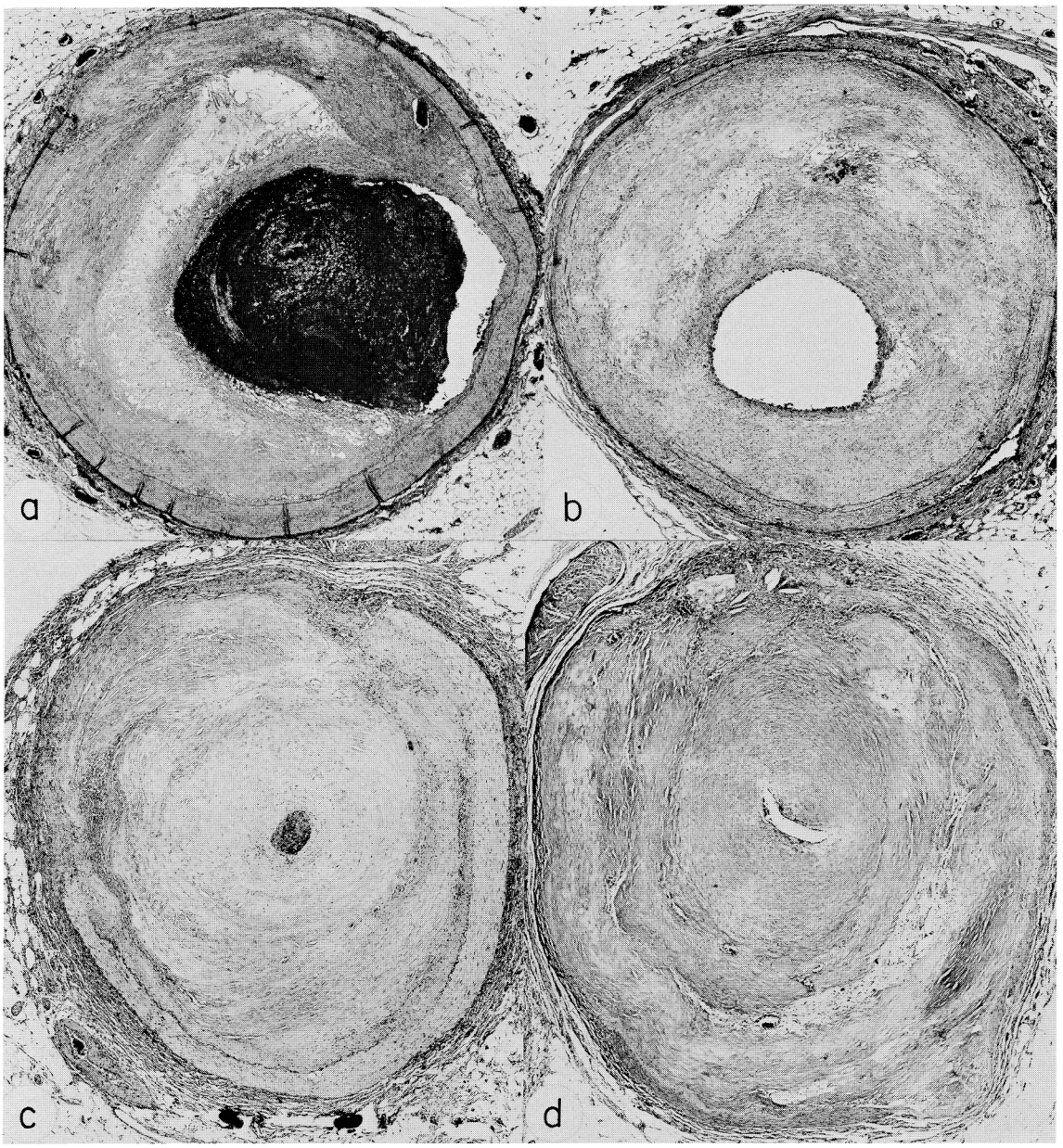

Figure 3

One coronary artery in each of two patients, both of whom had thrombi. (a *and* b) *Left circumflex coronary artery in a 57-year-old woman (A69-131) who died 4 days after onset of acute transmural myocardial infarction.* (a) *The thrombus is firmly attached to an old plaque. The retraction of the thrombus on one side is an artifact.* (b) *Distal to the thrombus, the lumen is > 75% narrowed by an old plaque. (Movat stains, each × 21.)*

(c *and* d) *Anterior descending coronary artery 6–7 cm from the aortic ostium in a 59-year-old woman (A68-285) who had the onset of acute transmural myocardial infarction 48 hours before death. She had the onset of intermittent chest pain 2 months earlier and systemic hypertension for 10 years. Her final 2 days were characterized by shock, pulmonary edema, and bradycardia. At autopsy, a "massive" anterior-wall infarct, which was aneurysmally dilated, was present. The lumens of all three major coronary arteries were >75% narrowed by old plaques. In addition, a small occluding thrombus was present in the left anterior descend-*

with ruptures of necrotic plaques is different from that unassociated with rupture. That coronary arterial thrombi are related to rupture of necrotic plaques, however, is far from proven. Serial sections are usually necessary to observe cracks in plaques, and even by this means interpretation is often difficult. Such cracks were infrequently observed beneath thrombi in the patients studied by Roberts and Buja, and probably most thrombi form over plaques with intact surfaces.[42, 43] Rupture of a plaque may result at times from cutting an artery and fixing it without prior support of its wall by injection. Fulton[43] injected coronary arteries with a solid supporting medium before sectioning, and in few did the intima produce convexity of the lining. In none of his 25 patients who died of coronary heart disease (14 with AMI) was ulceration of a plaque observed. Interpretation of whether a plaque is cracked or, if present, an artifact or real is fraught with too much difficulty, in my opinion, to give this possible mechanism of thrombosis undue weight.

The thrombus in fatal AMI is practically always located in the coronary artery responsible for supplying blood to the myocardium which was made necrotic: i.e., if the infarct involves the anterior wall of the left ventricle, and if a thrombus occurs, it will be located in the anterior descending coronary artery; posterior-wall necrosis is associated with thrombosis of the right coronary artery. When thrombi occur in either the left anterior descending or circumflex coronary arteries, they are usually located within 2 cm of the bifurcation of the left main (or within 4 cm of the left aortic) ostium. The left main artery is virtually never the site of thrombosis. The proximal portion of the right coronary artery, however, does not appear to be a more frequent site of thrombus formation than does the mid- or distal portion. Thrombi are infrequently seen in the small epicardial branches of the major extramural coronary arteries and never occur, other than as platelet aggregates, to my knowledge, in intramural coronary arteries. (See "Coronary Arterial Embolism" below, for comparison.)

Not all coronary arterial thrombi are totally occluding. (The term "occlusion" is not synonymous with "thrombosis" as implied in many reports, since occlusion may be partial as well as complete, and since the vessel may be occluded by material other than that which forms a thrombus.) Partially occluding mural or nonocclusive thrombi were found in seven (18%), and totally occluding (*occlusive*) thrombi in 33 (82%), of 40 patients with thrombi and fatal transmural myocardial necrosis studied by Roberts and Buja. Pure platelet thrombi, as mentioned earlier, are usually small and infrequently totally occlude lumens. Nonocclusive thrombi, since they are small, may have little functional significance. Even totally occluding thrombi when formed in arteries already >90% occluded by old atherosclerotic plaque also may have little functional significance. Thus, it is not enough to know whether or not a coronary artery contains a thrombus. Information regarding the degree of luminal narrowing by an old atherosclerotic plaque at the site of, and distal to, the thrombus, and whether the thrombus is totally or only partially occlusive is required before the significance of a coronary arterial thrombus can be judged.

The role of coronary thrombosis in AMI is unclear. For several decades coronary thrombosis was considered the cause of AMI. Clinically, AMI represents a sudden change for the patient compared to his preinfarction status. This often dramatic clinical event has been equated at autopsy with the finding of a "fresh" thrombus in a coronary artery. However, only about 50% of patients with transmural myocardial necrosis and about 10% of patients with subendocardial necrosis or "sudden cardiovascular collapse without necrosis"

ing vessel (c). *(Movat stain, × 25.) The percent of narrowing caused by the thrombus is small, however, compared to the percent of narrowing resulting from old atherosclerotic plaques. The lumen distal* (d) *to the thrombus is already severely narrowed by an old plaque. (Hematoxylin and eosin stain, × 25.)*

have a thrombus in a coronary artery at necropsy. Thus, nothing new is found in the coronary arteries in the majority of patients dying of cardiac disease. The lack of finding coronary arterial thrombi in patients dying suddenly of cardiac disease and in only about one half of those with myocardial necrosis has given rise to the concept that coronary arterial thrombi are *consequences* rather than *causes* of AMI. Comparison of histologic ages of coronary arterial thrombi and of acute myocardial infarcts has indicated to some observers[20] that thrombosis follows rather than precedes myocardial necrosis. Judging the age of a coronary thrombus, however, is difficult and probably inaccurate, and therefore this comparison is unreliable.

An examination of the clinical events during the period of myocardial infarction has provided a possible explanation for the occurrence of coronary arterial thrombi in some patients with AMI and their absence in others. Spain and Bradess[16, 28] have shown that the frequency of thrombi increased, up to a point, with increasing intervals between the onset of symptoms of myocardial ischemia and death, rising from 17% of 80 patients surviving < 1 hour, to 36% of 22 patients surviving 1–8 hours, and to 57% of 100 patients surviving > 8 hours. Thus, a certain but variable period of survival after infarction begins is usually necessary for a thrombus to form.

The presence of coronary arterial thrombi in AMI also has been found to correlate with the presence of the power-failure syndrome (a form of cardiogenic shock resulting in "an inability of the myocardium to maintain the level of cardiac output necessary for adequate organ perfusion. There is evidence of underperfusion of one or more organ systems").[30] Walston and associates[30] in a clinicopathologic study of 37 patients who died of AMI found thrombi in 17 (71%) of 24 patients with and in only two (15%) of 13 patients without the power-failure syndrome. Of their 37 patients, 19 had coronary arterial thrombi, 17 (90%) of whom had the power-failure syndrome; of their 18 patients without coronary arterial thrombi, seven (39%) had had the power-failure syndrome. Similar correlations between the presence of pump failure (shock or overt congestive cardiac failure or both) were observed by Roberts and Buja.[1] Thus, a severely diminished cardiac output and consequently slowed coronary arterial blood flow is usually required for a thrombus to form in a coronary artery. It has also been observed at necropsy that the larger the area of myocardial necrosis the more likely will a thrombus be present in a coronary artery. Of course, the larger the infarct, the more likely will pump failure occur.

The type of activity of patients at the time of onset of AMI also may reflect slowed blood flow. Master, Dack, and Jaffe[44] interviewed 890 patients with AMI and found that symptoms of myocardial necrosis appeared in 73% of them during sleep, rest, or mild activity (table 1). For myocardial necrosis to begin during inactivity is in direct contrast to angina pectoris, which appears during activity, but is associated with similar degrees of coronary arterial luminal narrowing.[4, 45–47] It would appear that decreased coronary arterial blood flow, i.e., relative stasis, is necessary for a thrombus to form in a coronary artery and that shock, congestive cardiac failure, and inactivity all decrease coronary flow. The slow-flow concept, however, does not explain the occurrence of coronary arterial thrombi at sites of, and proximal to, severe stenoses caused by old atherosclerotic plaques. Luminal narrowing, however, does introduce points

Table 1

Types of Activity at Onset of Acute Myocardial Infarction

Activity	Attacks	
	No.	%*
1. Sleep	198	22
2. Rest (lying or sitting)	277	31
3. Mild activity	180	20
4. Moderate activity (excludes walking)	76	9
5. Walking	141	16
6. Unusual or severe exertion	18	2
	890	100

*The percentages for these six activities are very similar to those occurring in most individual's daily lives.

of high-velocity gradients which appear to favor platelet aggregation.[48] A high shearing stress also may damage erythrocytes,[49] followed by release of adenosine diphosphate[50] and platelet damage.

Several explanations have been offered for the absence of coronary arterial thrombi in patients dying of AMI or of "acute cardiovascular collapse without myocardial necrosis." Postmortem lysis of thrombi as a result of excessive production of fibrinolysins has not been proved or disproved although several observations tend to discount this explanation. In fatal AMI or sudden death the major coronary arteries in patients without definite thrombi are frequently free of blood or blood products. If fresh thrombi had been lysed immediately postmortem, partially liquified blood or a remnant of a thrombus within the lumen would be expected, and this has not been the case. Necropsies performed within 15 min on patients with coronary heart disease dying suddenly have not disclosed evidence of partially lysed thrombi.[28] It is unlikely that postmortem lysis of thrombi could be so selective as to liquefy only those thrombi which allegedly might have been present in patients with subendocardial necrosis and not lyse those thrombi associated with transmural necrosis. It is unlikely that postmortem lysis, an artifact, which in a sense occurs by chance, could account for identical percentages of thrombi being present in separate but similar studies carried out a decade apart by the same investigators.[16, 28]

Inadequate examination of the coronary tree so that thrombi, though actually present, were not observed is highly unlikely. At least three histologic sections of every 5-mm segment of the entire extramural coronary arterial tree were examined in the study of 107 patients with fatal AMI by Roberts and Buja.[1] The chance of missing a thrombus by this technique is unlikely.

The absence of thrombi in coronary arteries of many patients with AMI may explain in part the lack of clear-cut benefits provided to patients with AMI treated with anticoagulants. After the use of these drugs for 20 years, controversy still continues as to whether or not they are beneficial to patients with AMI. Of factors favoring the use of anticoagulants in patients with AMI, the purported ability of these drugs to inhibit the formation or extension of a thrombus in a coronary artery has been high on the list. This factor, however, had been based on the supposition that AMI is usually caused by coronary thrombosis. The incidence of coronary arterial thrombi in fatal AMI in patients treated with anticoagulants is similar to that in patients not receiving anticoagulants.[6]

Although it may not be the precipitating cause of AMI, thrombosis may still cause the underlying coronary atherosclerosis. Indeed, there is little doubt that organization of thrombi contributes to the development of the complicated atherosclerotic plaque. The presence of fibrin and platelets in atherosclerotic plaques strongly connects atherosclerosis with thrombosis. Each has been found in plaques by immunofluorescent techniques,[51, 52] and fibrin is commonly found in plaques by histologic and electron-microscopic examination. Histologic evidence that a plaque is derived from a thrombus, however, is frequently obscured.[53] As a thrombus is covered by new endothelium, the underlying endothelium is replaced by connective tissue from the intima which obliterates the original line of demarcation (fig. 4). Thrombi appear to organize by ingrowth of overlying endothelial cells and by connective tissue from the intima.[54] Modified smooth-muscle cells,[55–57] which are capable of synthesizing collagen, elastin, and probably mucopolysaccharides[55, 58] and which are present in connective tissue of arterial intima (they also may be derived from endothelium[55]), invade the bases of attached thrombi. Small mural thrombi organize by an avascular process[53, 59] whereas larger thrombi become vascularized.[60] Capillaries extend from the new overlying endothelium to provide a direct blood supply from the lumen and from vasa vasora to penetrate thrombi at their bases.[60, 61] Vascularization is considered the hallmark of an organized thrombus.[60] Capillaries growing into a thrombus have

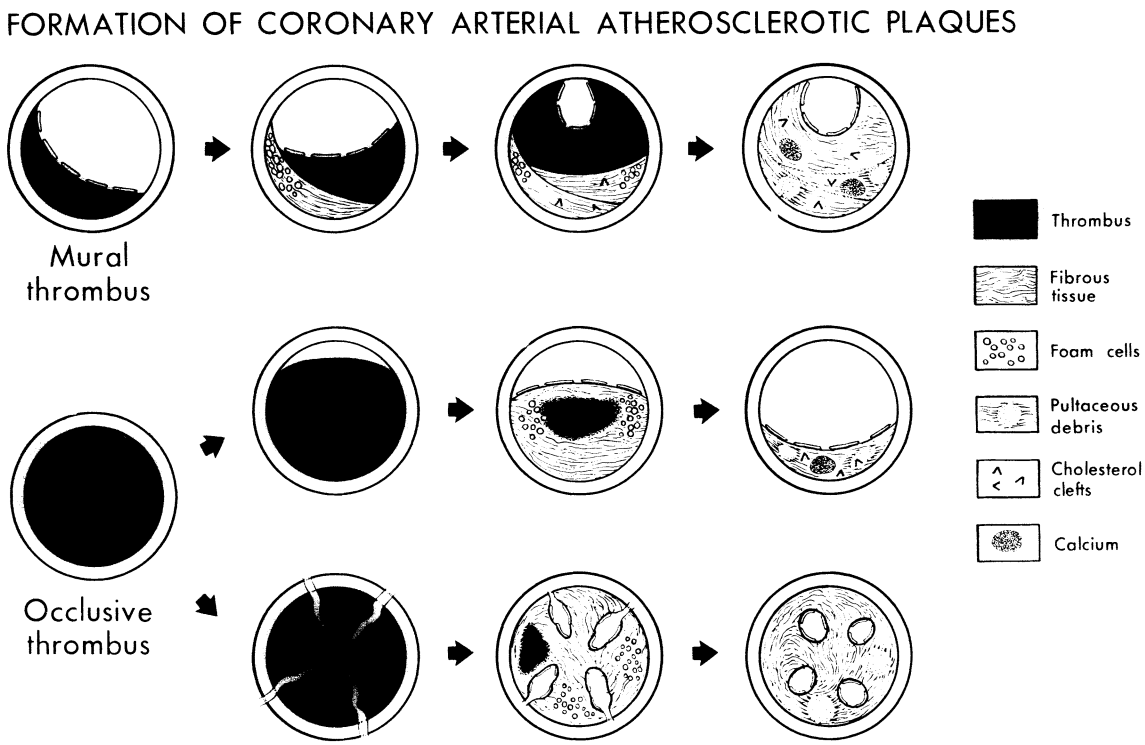

Figure 4

Diagram depicting formation of coronary arterial atherosclerotic plaques from mural and occlusive thrombi. The mural thrombus initially contacts only a portion of the intimal lining. The fibrin-platelet thrombus is covered by endothelial cells, and retraction occurs as it organizes into fibrous tissue. Foam cells appear. Another mural thrombus follows, and the process of organization is repeated. The lines of demarcation between the separate thrombi gradually fade so that at the final stage histologic study makes recognition of previous components of the thrombus difficult.

Organization of an occlusive thrombus may occur in two ways. In one, the thrombus retracts from one intimal surface to form a single channel. As it organizes, the surface of the thrombus exposed to the lumen is covered by endothelial cells. Organization takes place from the overlying newly grown endothelium and from preexisting intima to encase in fibrous tissue the residual thrombus, which may undergo fatty degeneration. Alternatively, organization may occur by capillaries growing into the thrombus at its base. The capillaries may dilate as the thrombus retracts during organization finally leading to the plaque with recanalized channels.

fibrinolytic activity,[62] which contributes to resolution of a thrombus as it organizes. These capillaries, which may later atrophy, can be a source of hemorrhage into plaques. Occlusive thrombi, like mural thrombi, may be incorporated into the intima of arteries as atherosclerotic plaques.[53] Occlusive thrombi may retract before endotheliazation is complete and thereby appear later as mural or nonocclusive plaques (fig. 4).

The source of lipids in atherosclerotic plaques is unclear. Fatty degeneration may occur in any thrombus or hematoma; organization of a left atrial thrombus in mitral stenosis, for example, may result in a structure apparently identical to an atherosclerotic plaque (fig. 5). Platelets, erythrocytes, and plasma all may provide lipids to plaques. When whole blood clots are injected into systemic veins of rabbits, fibrous intimal plaques (containing little lipid) form in pulmonary arteries.[63] Even though the emboli

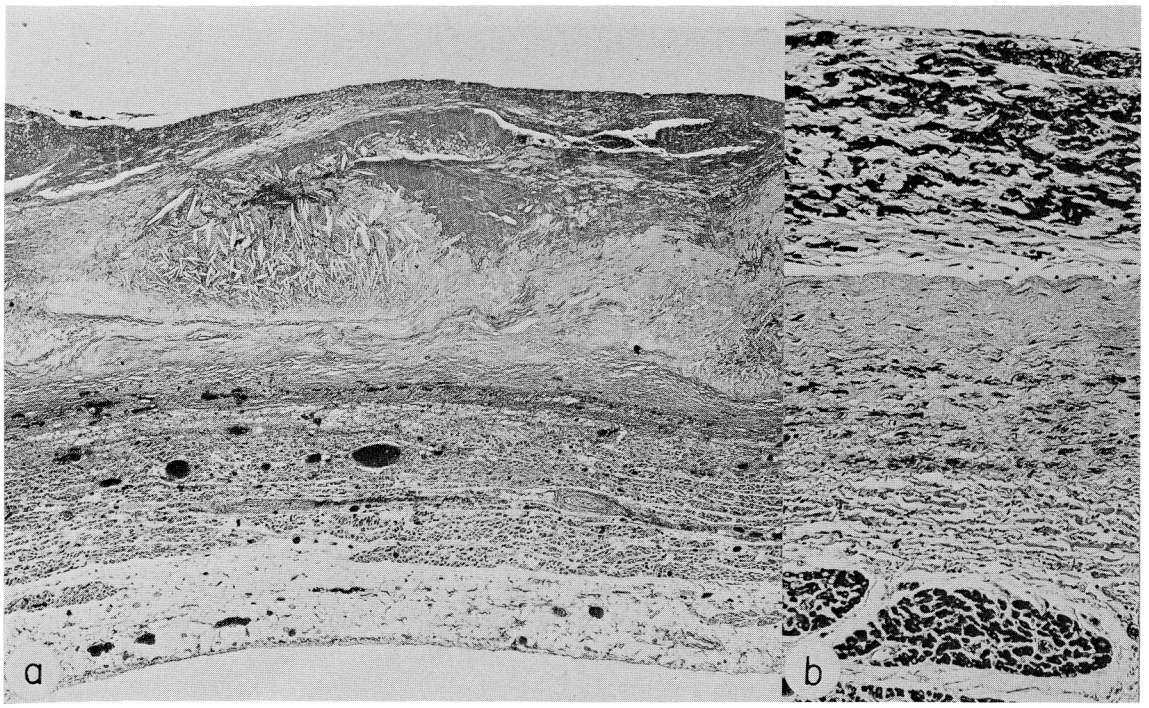

Figure 5

Left atrial thrombi in each of two patients with mitral valvular disease. Organization of these thrombi may result in plaques that may look identical to complicated atherosclerotic plaques. (a) *Section of left atrial wall in a 50-year-old woman (A67-210) with a huge thrombus. Organization of portions of the thrombus led to development of numerous cholesterol clefts, pultaceous debris, and calcific deposits, as well as fibrous tissue—components of arterial atherosclerotic plaques. (Hematoxylin and eosin stain, × 20.)*

(b) *Section of portion of left atrial wall in a 60-year-old man (A70-280) with severe mitral regurgitation. Mitral valve replacement was performed 50 days before death. Organizing mural thrombus was found in the left atrium at autopsy. The section shows strands of fibrin (dark) interspersed with strands of fibrous tissue (light) on the endocardial surface of the left atrium. This process represents organization of a thrombus—probably 50 days old—and is virtually identical to the fibrin-fibrous tissue lesions that occur in coronary arteries. (Phosphotungstic acid-hematoxylin stain, × 100.)*

are occlusive they organize by retracting into eccentric plaques. The conversion of thromboemboli to plaques is important evidence for the thrombotic origin of atherosclerosis. When platelet-rich thombi rather than whole blood clots are injected, typical fatty atherosclerotic plaques containing many foam cells and foci of calcium develop.[64] Erythrocytes contain less lipid than do platelets, but repeated small hemorrhages may lead to accumulation of large amounts of lipid, especially cholesterol.[65] The plasma supplies lipoproteins, which are found in both recent and organizing thrombi[66] as well as in old plaques.[67]

Atherosclerotic plaques are like fingerprints. No two are alike. In a study of the entire coronary tree of 107 patients with fatal AMI, tremendous variation in the composition of adjacent plaques was noted.[1] Some plaques contained lipid and large quantities of pultaceous debris, whereas others were composed primarily of fibrous tissue. Differences in composition of original thrombi may explain differences in composition of atherosclerotic plaques. Mixed white and red thrombi form plaques that contain some foam cells,[68] but not in the quantity found in plaques derived from platelet-rich or white thrombi.[64] The

type of thrombus, whether mural (nonocclusive) or occlusive, also may affect the composition of a plaque. Occlusive platelet thrombi usually do not accumulate fibrin while undergoing transformation to fibrofatty plaques.[64] Mural platelet thrombi, in contrast, appear to be partially or totally replaced by fibrin before undergoing organization, and consequently the plaques that form are mainly fibromuscular.[69-71]

Hemorrhages into Atherosclerotic Plaques

Hemorrhages into old atherosclerotic plaques are common, occurring in 26 (24%) of 107 patients studied by Roberts and Buja,[1] but they probably are of little functional significance. In only one of the 26 patients with hemorrhages into plaques studied by Roberts and Buja did the lumen of the artery appear to have been compromised by the extravasated blood. In contrast to thrombi in coronary arteries in fatal AMI, hemorrhages often occur in coronary arteries unrelated to the area of necrosis, and they may occur in more than one artery or in multiple sites in the same artery. Hemorrhages appear to form from either breaks in the fibrous capsule covering a plaque or from rupture of a small vascular channel within a plaque. Each of these mechanisms is difficult to prove in the individual patient. Possibly small hemorrhages into old plaques occur chronically and have little to do with AMI. It is possible that some hemorrhages into old plaques may be produced artifactually during cutting and processing of coronary arteries for histologic study. A possible detrimental effect of hemorrhages into plaques is the occurrence of superimposed thrombi. This association, however, is not as frequent as once supposed. The two may occur together, presumably when a crack in a plaque is the responsible mechanism. Fulton,[43] Jørgensen et al.,[6] and Roberts and Buja[1] did not find an association between hemorrhages into plaques and coronary thrombosis, probably because the majority of thrombi were observed over plaques that consisted predominantly of fibrous tissue.[43] The incidence of hemorrhages into plaques does not appear to be increased by the use of anticoagulants.[6, 43]

Coronary Arterial Embolism

The occurrence of a clot in the distal portion of a major extramural coronary artery suggests that the cause is embolism rather than thrombosis. This situation occurred in three of 107 patients with fatal AMI studied by Roberts and Buja. Coronary arterial embolism differs from thrombosis in the following manner: (1) the clot is located distally, not proximally, and is usually in the anterior descending coronary artery; (2) the clot extends into intramural coronary arteries and into the epicardial branches of the major extramural vessel (in thrombosis, no clot is found in intramural coronary arteries and uncommonly in the small epicardial branches of major vessels); and (3) the entire extramural coronary arterial tree is relatively free of old atherosclerotic plaques. It is difficult to make the diagnosis of embolism anatomically if the lumens of the coronary arteries are >50% narrowed by old plaque. Also, patients with emboli are usually relatively young and the predisposing circumstances exist for embolism to occur (arrhythmia, infective endocarditis, intracardiac mural thrombosis, etc.).[72-76]

Intramural Coronary Arteries in Fatal AMI

Much has been written about disease of the small coronary arteries. That intramural coronary arteries are narrowed in certain conditions, particularly the neurogenic heart diseases (Friedrich's ataxia, progressive muscular dystrophy, myotonic congenita), is now a well-established fact.[77] In my view, conditions that involve extramural coronary arteries have not been shown also to involve the intramural coronary arteries. There are dissenting views, however, on this point.[78-81] Likewise, conditions that clearly involve intramural coronary arteries tend to spare the extramural coronary arteries. With the exception of the small arteries in the left ventricular papillary muscles, which are subjected to maximal systolic intraventricular pressure over the entire circumference of their surfaces, diseases

that affect the intramural coronary arteries do not affect the extramural coronary arteries, and vice versa. Other than insignificant minimal fibrous intimal proliferation in a rare intramural coronary artery, and that usually is in the left ventricular papillary muscles, no abnormality was observed in the intramural coronary arteries in any of the 107 patients with fatal AMI studied by Roberts and Buja. Indeed the intramural vessels in the heart appear to be protected from intimal proliferation and luminal narrowing by the contracting adjacent myocardium. In coronary atherosclerosis, plaques occur routinely in epicardial branches of major extramural arteries, but as soon as these branches penetrate into myocardium the lumen is suddenly wide open again. Even in systemic hypertension, the intramural coronary arteries are not affected as are other small systemic arteries in this condition. The coronary arteries are not exposed to the high systolic pressure because they are perfused mainly in diastole. The contracting ventricular myocardium may further lower the intraluminal pressure in these small vessels. Although patients with diabetes mellitus have been reported to have disease of intramural coronary arteries,[79] this finding has not been observed by this author. Foam cells, cholesterol clefts, and pultaceous debris—components of plaques in extramural coronary arteries—are virtually never found in intramural vessels. Thus, significant involvement of intramural coronary arteries does not occur in patients with significant luminal narrowing of extramural coronary arteries.

References

1. Roberts WC, Buja LM: The frequency and significance of coronary arterial thrombi and other observations in fatal acute myocardial infarction: A study of 107 necropsy patients. Amer J Med. In press
2. Brice JG, Dowsett DJ, Lowe RD: The effect of constriction on carotid bloodflow and pressure gradient. Lancet **1**: 84, 1964
3. Saphir O, Priest WS, Hamburger WM, Katz LN: Coronary arteriosclerosis, coronary thrombosis and the resulting myocardial changes. Amer Heart J **10**: 567, 1935
4. Blumgart HL, Schlesinger MJ, Davis D: Studies on the relation of the clinical manifestations of angina pectoris, coronary thrombosis, and myocardial infarction to the pathologic findings with particular reference to the significance of the collateral circulation. Amer Heart J **19**: 1, 1940
5. Yater WM, Traum AH, Brown WG, Fitzgerald RP, Geisler MA, Wilcox BB: Coronary artery disease in men 18 to 39 years of age: Report of 866 cases, 450 with necropsy examination. Amer Heart J 36: 334, 481, 683, 1948
6. Jørgensen L, Chandler AB, Borchgrevink CF: Acute lesions of coronary arteries in anticoagulant-treated and in untreated patients. Atherosclerosis **13**: 21, 1971
7. Classification of atherosclerotic lesions. Report of a Study Group, WHO Techn Rep Ser (no. 143), 1958
8. Roberts WC, Levy RI, Fredrickson DS: Hyperlipoproteinemia: A review of the five types with first report of necropsy findings in type 3. Arch Path (Chicago) **90**: 46, 1970
9. Frink RJ, Achor RWP, Brown AL Jr, Kincaid OW, Brandenberg RO: Significance of calcification of the coronary arteries. Amer J Cardiol **26**: 241, 1970
10. Barnes AB, Ball RG: The incidence and situation of myocardial infarction in one thousand consecutive postmortem examinations. Amer J Med Sci **183**: 215, 1932
11. Lisa JR, Ring A: Myocardial infarction or gross fibrosis: Analysis of 100 necropsies. Arch Intern Med (Chicago) **50**: 131, 1932
12. Friedberg CK, Horn H: Acute myocardial infarction not due to coronary artery occlusion. JAMA **112**: 1675, 1939
13. Foord AG: Embolism and thrombosis in coronary heart disease. JAMA **138**: 1009, 1948
14. Miller RD, Burchell HB, Edwards JE: Myocardial infarction with and without acute coronary occlusion: A pathologic study. Arch Intern Med (Chicago) **88**: 597, 1951
15. Branwood AW, Montgomery GL: Observations on the morbid anatomy of coronary artery disease. Scot Med J **1**: 367, 1956
16. Spain DM, Bradess VA: Frequency of coronary thrombi as related to duration of survival from onset of acute fatal episodes of myocardial ischemia. Circulation **22**: 816, 1960

17. Spain DM, Bradess VA: The relationship of coronary thrombosis to coronary atherosclerosis and ischemic heart disease: A necropsy study covering a period of 25 years. Amer J Med Sci **240**: 701, 1960
18. Kurland GS, Weingarten C, Pitt B: The relation between the location of coronary occlusions and the occurrence of shock in acute myocardial infarction. Circulation **31**: 646, 1965
19. Meadows R: Coronary thrombosis and myocardial infarction. Med J Australia **2**: 409, 1965
20. Ehrlich JC, Shinohara Y: Low incidence of coronary thrombosis in myocardial infarction: A restudy by serial block technique. Arch Path (Chicago) **78**: 432, 1964
21. Mitchell JRA, Schwartz CJ: Arterial Disease. Philadelphia, F.A. Davis, 1965
22. Baroldi G: Acute coronary occlusion as a cause of myocardial infarct and sudden coronary heart death. Amer J Cardiol **16**: 859, 1965
23. Harland WA, Holburn AM: Coronary thrombosis and myocardial infarction. Lancet **2**: 1158, 1966
24. Kagan A, Livsic AM, Sternby N, Vihert AM: Coronary-artery thrombosis and the acute attack of coronary heart-disease. Lancet **2**: 1199, 1968
25. Chapman I: Relationships of recent coronary artery occlusion and acute myocardial infarction. J Mt Sinai Hosp **35**: 149, 1968
26. Jørgensen L, Hoerem JW, Chandler AB, Borchgrevink CF: The pathology of acute coronary death. Acta Anaesth Scand (suppl) **29**: 193, 1968
27. Hackel DB, Estes EH, Walston A, Koff S, Day E: Some problems concerning coronary artery occlusion and acute myocardial infarction. Circulation **40** (suppl IV): IV-31, 1969
28. Spain DM, Bradess VA: Sudden death from coronary heart disease: Survival time, frequency of thrombi, and cigarette smoking. Dis Chest **58**: 107, 1970
29. Bouch DC, Montgomery GL: Cardiac lesions in fatal cases of recent myocardial ischemia from a coronary care unit. Brit Heart J **32**: 795, 1970
30. Walston A, Hackel DB, Estes EH: Acute coronary occlusion and the "power failure" syndrome. Amer Heart J **79**: 613, 1970
31. Edwards JE: What is myocardial infarction? Circulation **40** (suppl IV): IV-5, 1969
32. Jørgensen L: Experimental platelet and coagulation thrombi: A histologic study of arterial and venous thrombi of varying age in untreated and heparinized rabbits. Acta Path Microbial Scand **62**: 189, 1964
33. Leary T: Coronary spasm as a possible factor in producing sudden death. Amer Heart J **10**: 338, 1934
34. Clark E, Graef I, Chasis H: Thrombosis of the aorta and coronary arteries: With special reference to the fibrinoid lesions. Arch Path (Chicago) **22**: 183, 1936
35. Osborn GR: The Incubation Period of Coronary Thrombosis. London, Butterworths, 1963
36. Chapman I: Morphogenesis of occluding coronary artery thrombosis. Arch Path (Chicago) **80**: 256, 1965
37. Constantinides P: Plaque fissures in human coronary thrombosis. J Atheroscler Res **6**: 1, 1966
38. Friedman M, Van den Bovenkamp GJ: The pathogenesis of a coronary thrombus. Amer J Path **48**: 19, 1966
39. Jørgensen L: Thrombosis and the complications of atherosclerosis. *In*: Atherosclerois, Proceedings of the Second International Symposium, edited by RJ Jones. New York, Springer-Verlag, 1970
40. Friedman M: The coronary thrombus: Its origin and fate. Human Path **2**: 81, 1971
41. Hovig T, Jørgensen L, Packham MA, Mustard JF: Platelet adherence to fibrin and collagen. J Lab Clin Med **71**: 29, 1968
42. Anitschkow N: Morphodynamik der Koronarsklerose des Herzens. Acta Path Microbiol Scand **49**: 426, 1960
43. Fulton WFM: The Coronary Arteries: Arteriography, Microanatomy, and Pathogenesis of Obliterative Coronary Artery Disease. Springfield, Illinois, Charles C Thomas, 1965
44. Master AM, Dack S, Jaffe HL: Activities associated with the onset of acute coronary artery occlusion. Amer Heart J **18**: 434, 1939
45. Zoll PM, Wessler S, Blumgart HL: Angina

pectoris, clinical and pathologic correlations. Amer J Med **11**: 331, 1951

46. Lenegre J, Himbert J: Critical study of the relationship between angina pectoris and coronary atherosclerosis. Amer Heart J **58**: 539, 1959
47. Allison RB, Rodriguez FL, Higgins EA Jr, Leddy JP, Abelmann WH, Ellis LB, Robbins SL: Clinicopathologic correlations in coronary atherosclerosis: Four hundred thirty patients studied with postmortem coronary angiography. Circulation **27**: 170, 1963
48. Dintenfass L, Rozenberg MC: The influence of the velocity gradient on *in vitro* blood coagulation and artificial thrombosis. J Atheroscler Res **5**: 276, 1965
49. Nevaril CG, Lynch EC, Alfrey CP Jr, Hellums JD: Erythrocyte damage and destruction induced by shearing stress. J Lab Clin Med **71**: 784, 1968
50. Harrison MJG, Mitchell JRA: The influence of red blood-cells on platelet adhesiveness. Lancet **2**: 1163, 1966
51. Woolf N, Crawford T: Fatty streaks in aortic intima studied by an immuno-histochemical technique. J Path Bact **80**: 405, 1960
52. Woolf N, Carstairs KC: Infiltration and thrombosis in atherosclerosis: A study using immunofluorescent techniques. Amer J Path **51**: 373, 1967
53. Duguid JB: Thrombosis as a factor in the pathogenesis of coronary atherosclerosis. J Path Bact **58**: 207, 1946
54. Crawford T, Levene CI: Incorporation of fibrin in the aortic intima. J Path Bact **64**: 523, 1952
55. Haust DM, More RH, Movat HZ: The role of smooth muscle cells in the fibrogenesis of arteriosclerosis. Amer J Path **37**: 377, 1960
56. Geer JC, McGill HC Jr, Strong JP: The fine structure of the human atherosclerotic lesions. Amer J Path **31**: 263, 1961
57. Wissler RW: The arterial medial cell, smooth muscle or multifunctional mesenchyme? J Atheroscler Res **8**: 201, 1968
58. Getz GS, Vesselinovitch D, Wissler RW: A dynamic pathology of atherosclerosis. Amer J Med **46**: 657, 1969
59. Haust MD, More RH, Movat HH: The mechanism of fibrosis in arteriosclerosis. Amer J Path **35**: 265, 1959
60. Geiringer E: Intimal vascularization and atherosclerosis. J Path Bact **63**: 201, 1951
61. Morgan AD: The Pathogenesis of Coronary Occlusion. Springfield, Illinois, Charles C Thomas, 1956
62. Todd AS: Localization of fibrinolytic activity in tissues. Brit Med Bull **20**: 210, 1964
63. Harrison CV: Experimental pulmonary atherosclerosis. J Path Bact **60**: 289, 1948
64. Hand RA, Chandler AB: Atherosclerotic metamorphosis of autologous pulmonary thromboemboli in the rabbit. Amer J Path **40**: 469, 1962
65. Hartroft WS: Ceroid-like pigments, hemoceroid and hyaloceroid, in atheromatous lesions of human subjects. Amer J Path **28**: 526, 1952
66. Woolf N, Pilkington TRE, Carstairs KC: The occurrence of lipoproteins in thrombi. J Path Bact **91**: 383, 1966
67. Kao VCY, Wissler RW: A study of the immunohistochemical localization of serum lipoproteins and other plasma proteins in human atherosclerotic lesions. Exp Molec Path **4**: 457, 1965
68. Filshie I, Scott GBD: The organization of experimental venous thrombi. J Path Bact **76**: 71, 1958
69. Jørgensen L, Rowsell HC, Hovig T, Mustard JF: Resolution and organization of platelet-rich mural thrombi in carotid arteries of swine. Amer J Path **51**: 681, 1967
70. Woolf N, Bradley JWP, Crawford T, Carstairs KC: Experimental mural thrombi in the pig aorta: The early natural history. Brit J Exp Path **49**: 257, 1968
71. Woolf N, Castairs KG: The survival time of platelets in experimental mural thrombi. J Path **97**: 595, 1969
72. Saphir O: Coronary embolism. Amer Heart J **8**: 312, 1933
73. Hamman L: Coronary embolism. Amer J Med **21**: 401, 1941
74. Shrader EL, Bawell MB, Moragues V: Coronary embolism. Circulation **14**: 1159, 1956
75. Wenger NK, Bauer S: Coronary embolism: Review of the literature and review of fifteen cases. Amer J Med **25**: 549, 1958

76. Oakley C, Yusuf R, Hollman A: Coronary embolism and angina in mitral stenosis. Brit Heart J **23:** 357, 1961

77. James TN: Etiologic concept concerning the obscure myocardiopathies. Progr Cardiovasc Dis **7:** 43, 1964

78. Saphir O, Ohringer L, Wong R: Changes in the intramural coronary branches in coronary arteriosclerosis. Arch Path (Chicago) **62:** 159, 1956

79. Blumenthal HT, Alex M, Goldenberg S: A study of lesions of the intramural coronary artery branches in diabetes mellitus. Arch Path (Chicago) **70:** 13, 1960

80. Donomae I, Matsumoto Y, Kokubu T, Koide R, Kobayashi R, Ikegami H, Ueda E, Fujisawa T, Fujimoto S: Pathological studies of coronary atherosclerosis: Especially of sclerosis of intramuscular coronary arteries. Jap Heart J **3:** 423, 1962

81. More BM, Sommers SC: The status of the myocardial arterioles in angina pectoris. Amer Heart J **64:** 323, 1962