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Characteristics of the plaque under a coronary thrombus

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Summary. Young men dying suddenly and autopsied by the coroner sometimes have coronary thrombosis at a relatively early stage of arteriosclerosis. The plaques under such thrombi often have a complex of features, a) rupture, b) hemorrhage, c) medial destruction, d) nodular collections of foam cells, e) calcification, f) cellular infiltrates of the fibrous cap, fibrous base and adventitia, and g) a newly described kind of phagocytic activity at the boundary between the necrotic core and the fibrous base of the plaque. Commonplace innocuous plaques in most middle and old aged subjects without heart disease also often have some of these features. What structural characteristics might distinguish rare thrombogenic from commonplace innocuous plaques? Twenty-one thrombotic plaques from 18 cases of sudden coronary heart disease (CHD) death were histologically compared with 129 nonthrombotic plaques from these same 18 cases, 85 plaques from 23 cases of CHD death due to arteriosclerotic occlusion, and 94 plaques from 22 cases having no CHD. Plaques with thrombosis all had necrotic cores; plaques for comparison with these were therefore chosen all to have necrotic cores. Rupture and hemorrhage were found in 90% of thrombotic plaques, with mixing of plaque gruel and blood in the thrombus. Medial destruction, foam cells and calcification (features c, d, and e) were commonplace in all types of plaques. Small-cell infiltrates and atherophagocytosis (features f or g) were found in 72–94% of the 21 thrombotic plaques, but only in 18–24% of the 94 not CHD plaques. The necrotic core, characterized by crystalline cholesterol, appears to incite cellular responses in some plaques but not others; those responses distinguish thrombogenesis. The findings imply that thrombogenicity and its accompanying plaque cellularity are incited not by cholesterol, but by some trace or minor component of the plaque gruel of the necrotic core. The possibility of testing these hypotheses by practical methods has been shown to be feasible.

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Introduction

In 1928, Boyd noted that, "... in most cases of coronary thrombosis there is an underlying arteriosclerosis forming the basic lesion upon which the thrombus is formed ... It is evident that a coronary artery may remain sclerosed for years without thrombosis and there must be some mechanism which eventually incites the deposit of platelets and fibrin". Since that time, a number of studies have been reported attempting to explain why some atherosclerotic lesions seem to be more dangerous than others. These reports are surveyed here to help define what structural characteristics to look for in a comparison of thrombotic with nonthrombotic coronary plaques.

A clear distinction is usually possible to make between plaques which do not and plaques which do have a necrotic core characterized by crystalline cholesterol (Tracy et al. 1983). "It is the latter type which may produce occlusion of the vessel by discharge of the soft pultaceous material or it may lead by ulceration to the formation of occlusive thrombus" (Branwood and Montgomery 1956). The fact that a necrotic core in the plaque is a *sine qua non* for coronary thrombosis has been described in several series of cases (Chapman 1965; Constantinides 1966; Friedman 1971), and has been implied without explicit description in others (Clark et al. 1936; Crawford et al. 1961; Davies and Thomas 1981; Davies et al. 1976; Falk 1983; Jorgenson et al. 1971; Leary 1934; Roberts and Buja 1972; Schwartz and Mitchell 1962; Yater et al. 1948). Oddly, this fundamental fact has not been specifically stated by any of these authors, as if its truth were self evident and required no comment.

The occurrence of plaque rupture as a common initiating event in thrombosis has long been recognized (Chapman 1965; Clark et al. 1936; Constantinides 1966; Crawford et al. 1961; Davies and Thomas 1981; Davies et al. 1976; Falk 1983; Friedman 1971; Jorgenson et al. 1971; Leary 1934; Roberts and Buja 1972; Schwartz and Mitchell 1962; Yater et al. 1948). "Rupture of an atheromatous cavity into the lumen or the rare reverse process, rupture from the lumen into the cavity, is the standard terminal lesion in older persons." (Leary 1934). Although this is a dominant mechanism, uncertainty revolves around the minority of cases in which rupture cannot be demonstrated. Some authors maintain that serial sectioning will reveal at least a tiny fissure in every case (Chapman 1965; Constantinides 1966; Friedman 1971). However, the meaning of this, even if true, is not clear. "Thrombosis of non-ruptured plaque was often found in association with small intimal breaks, but these had not led to the opening of a large necrotic core... Whatever the mechanism of thrombosis in these cases, the difference in structure of this lesion from thrombosis of ruptured plaque was so striking that we grouped the two types of lesions separately". (Jorgenson et al. 1971).

However this issue may eventually be resolved, a further question must still be confronted. "What takes place in a vessel that has been diseased for decades and leads to its occlusion by a thrombus at a given instant in time?" (Friedman 1974). Constantinides (1966) has suggested that, "Any structural weakening of the atherosclerotic lining from whatever cause (cell depopulation, necrosis, physical or chemical collagen changes) could conceivably progress to the point where the lining would be fractured by the rhythmic beating of even the normal pulse waves".

Accompanying the necrotic core, a focal, nodular infiltrate of foam cells is very often present under the thrombus in the fibrous cap of an unruptured plaque or mixed with plaque gruel, fibrin and platelets in the thrombus over a ruptured plaque (Chapman 1965; Constantinides 1966; Friedman 1971). This conspicuous characteristic of thrombotic plaque is not mentioned by most authors, as if it were unconsciously subsumed under the term "atheroma". Friedman (1971) states that, "... masses of these cells may infiltrate the dense hyalinized cap of the plaque, converting it into a friable spongy mass, which is very liable to fracture. It is quite probable that the grumous or pultaceous contents of the abscesses build up their own invasive or corrosive potentiality similar to that exhibited by a cholesteatoma of the middle ear." Thus, these nodular foci of foam cells may in some way indicate an erosive activity that accompanies an expansion of the necrotic core.

Many authors have emphasized the possible importance of infiltration by cells of an apparently inflammatory nature (Chapman 1969; Klotz 1910; Parums and Mitchinson 1981; Saphir 1955; Schwartz and Mitchell 1962; Zak et al. 1955). By analogy with syphilitic aortitis, "Sumikawa, in 1903, stressed that in instances of perivascular inflammations the intima may show most severe changes, although the media and adventitia may show only slight alterations. He produced intimal proliferations experimentally by injecting turpentine close to vessels and also by bacterial injections" (Saphir 1955). In a systematic study of adventitial cellularity of apparent lymphocytic composition, Schwartz and Mitchell (1962) found, "In artery blocks without thrombus, and with recanalizing thrombus, the relationship between plaque severity and the grade of adventitial cellularity was similar to that in the random male population, but in arteries with recent thrombus this relationship was modified considerably, the prevalence of adventitial cellularity being significantly higher than that in the random male sample..." The presence of inflammatory cells within the various parts of the plaque has often been mentioned, but systematically studied only in the adventitia.

As the necrotic core expands, the associated media withers and the plaque is able to bulge outward into epicardial fat. Crawford and Levene (1953) have suggested that perhaps, "... the atheromatous area becomes comparable to a minute shallow wide-mouthed aneurysm in which mural thrombosis and organization proceed; and the atheromatous aneurysm becomes not, as it is usually regarded, a rare complication of atheroma, but merely an exceptionally severe lesion. In this way the triad of atheroma,

thrombosis and aneurysm becomes linked in one continuous pathological process."

A newly recognized plaque component has recently been described (Tracy 1984). At the boundary between the necrotic core and the fibrous base of the plaque, dense clusters of cells are apparently involved in atherophagocytosis. Small cholesterol crystals are contained within cells, and larger crystals are covered by cells which seem to flow together into a syncytium. They resemble the foam cells of the fibrous cap, but are subtly different by having a more compact, amphophillic cytoplasm. It was suggested that this feature may distinguish thrombogenic plaques. In the report of Yater et al. (1948, Figure 16) this appearance was illustrated photographically but not described or emphasized as a distinctive feature of thrombogenic plaques.

Coronary plaques are commonplace in almost everyone after age 45–50. In the absence of thrombosis or heart disease these have been called "inert" (Branwood and Montgomery 1956), "quiescent" (Friedman 1971) or "innocuous" (Tracy 1984). Does the plaque under a thrombus differ structurally from the quiescent ones? In a comparison between plaques that underlie a thrombus and innocuous plaques, some important features to examine are a) rupture, b) hemorrhage, c) medial destruction, d) nodular collections of foam cells in the fibrous cap, e) small cell infiltrates in the fibrous cap, f) cell infiltrates in the fibrous base, g) cell infiltrates in the adventitia and h) phagocytosis at the necrosis-base boundary. To this list can be added i) calcification. No series of cases has been assembled to assess these features simultaneously. The present study was carried out, therefore, to explore the feasibility of such an undertaking.

Patients and methods

Selection of cases. Over an 18 month period of performing autopsies for the Orleans Parish Coroner, the pathologist retained specimens in 41 out of 63 deaths due to coronary heart disease (CHD) under age 65. These CHD cases were classed at the time of gross dissection into those having acute thrombosis (18 cases) and those having arteriosclerotic occlusion and myocardial scars without thrombosis (23 cases). No case with arteriosclerotic occlusion was accepted without conspicuous myocardial scars. Most cases of thrombosis also had arteriosclerotic stenoses of the coronaries and myocardial scars, and the scars were often in the region of the heart supplied by the thrombotic artery. The cases of coronary thrombosis were matched by age, race and sex as closely as possible within the available time with a comparison group of 22 cases having no cardiovascular disease. After microscopic examination, 8 cases of arteriosclerotic occlusion were found to have 11 thrombotic plaques; these plaques are treated separately in Table 2, and combined into a group of all 32 thrombotic plaques in Table 3. In two cases, thrombus was not in a major coronary branch, but was found in a small branch not usually included in step-section techniques. In two other cases, microscopy missed the thrombus, but these cases were retained as thrombosis deaths.

Gross dissection. Coronary arteries were opened longitudinally on the fresh unopened heart. Thrombosis was recognized by the presence of a translucent, gray, soft mass, sometimes with variable amounts of pink or red coloration in alternating layers. These were always found at points of severe, focal narrowing of the coronary lumen, usually by a plaque which was grossly seen to contain plaque gruel. The thrombus was adherent to the plaque, but often

Table 1. Numbers of coronary heart disease cases having and not having coronary thrombus in two series of collections[a]

	Age	Thrombus			No thrombus			Percent with thrombus		
		Male	Female	Total	Male	Female	Total	Male	Female	Total
First	<45	9	0	9	0	0	0	100	–	100
series	45–54	15	1	16	7	0	7	68	100	70
	55–64	10	4	14	7	6	13	59	40	52
Second	<45	11	2	13	3	0	3	79	100	81
series	45–54	11	1	12	7	0	7	61	100	63
	55–64	7	3	10	9	9	18	44	25	36
Combined	<45	20	2	22	3	0	3	87	100	88
series	45–54	26	2	28	14	0	14	65	100	67
	55–65	17	7	24	16	15	31	52	32	44

[a] First series was previously reported (Tracy 1983). Second series is the one surveyed for this report. The two were assembled in the same source at different time periods

Table 2. Percentage of various features in plaques having thrombosis with or without widespread arteriosclerotic occlusion

Plaque feature	Thrombus only (%)	Thrombus plus arteriosclerotic occlusion (%)	All thrombotic plaques (%)
Hemorrhage	90	73	84
Rupture	86	73	81
Deep cellularity	100	82	94
Phagocytosis	71	82	75
Superficial cellularity	62	91	72
Adventitial infiltrate	71	82	75
Foam cells	86	91	88
Medial erosion	76	91	82
Calcification	29	36	31
Number of plaques	21	11	32
Number of cases	18	8	26

parts of it washed away in a gentle stream of water. Hearts with myocardial scars often had severe, widespread calcific narrowing which prevented opening of the tiny residual lumen. These coronary segments were processed without opening.

Processing of tissue. The left, right and anterior descending coronary arteries opened longitudinally were dissected from the heart, flattened on cardboard and fixed in formalin. The thrombus was sampled together with 1 cm proximal and distal. In vessels not having thrombus, the worst looking plaque together with 1 cm proximal and distal was sampled. The three segments of 2 cm length each were decalcified routinely in 1% acetic acid for three days, blocked in paraffin, sectioned at 6 μm thickness and stained with haematoxylineosin. Segments blocked in longitudinal orientation were cut perpendicular to the intimal surface in steps of 0.48 mm through the block (stepping through the circumferential dimension).

Table 3. Percentages of various features in plaques having thrombus and in nonthrombotic necrotic plaques for three cause-of-death groups

Plaque feature	All combined	Nonthrombotic plaques in cause-of-death groups			
	Thrombotic plaques[a] (%)	Thromboses[b] (%)	Arteriosclerotic occlusion[c] (%)	Not CHD (%)	Difference in percentage[d]
Hemorrhage	84	32	6	7	77
Rupture	81	24	4	5	76
Deep cellularity	94	60	27	24	70
Phagocytosis	75	42	6	18	57
Superficial cellularity	72	41	7	22	50
Adventitial infiltrate	75	45	28	26	49
Foam cells	88	63	14	53	35
Medial erosion	82	62	72	51	31
Calcification	31	33	76	43	−12
Number of plaques	32	129	85	94	
Number of cases	26	18	23	22	

[a] These 32 plaques include 21 from the 18 cases who died of thrombosis and 11 found incidentally in cases who died of arteriosclerotic occlusion

[b] Thrombotic plaques excluded; these are the non-thrombotic plaques in thrombosis death cases

[c] Thrombotic plaques excluded; these are the non-thrombotic plaques in 23 arteriosclerotic occlusion death cases

[d] Column 1 minus column 4 represents the contrast between thrombotic plaques and necrotic plaques in cases not having coronary heart disease

Evaluation of sections. The features to be assessed are illustrated in Fig. 1, in which a typical thrombogenic plaque is used to exemplify a kind of composite of the distinctive characteristics of those plaques which had thrombosis. Recorded as present or absent were thrombosis, rupture of cap, foam cell collections in the cap, superficial dense collections of small cells, hemorrhage, phagocytic cells at the necrotic core-fibrous base junction, deep dense collections of small cells, erosion through the media of the plaque into the adventitia, adventitial infiltration of small cells or mixed inflammatory cells, and calcification. Each segment of artery was scanned at each of the steps through its circumference, and each place having a necrotic core was evaluated as a plaque, up to 3 "plaques" per segment. For each plaque, the evaluated features were noted as present if found anywhere in the circumferential step sections.

Results

Kinds of CHD. At the time of autopsy, each case of coronary heart disease could usually be clearly classified as thrombosis or as widespread calcific

Fig. 1. A thrombotic coronary plaque is not ruptured or hemorrhagic but illustrates other features of a typical plaque beneath a coronary thrombus, *1)* thrombus, *2&3)* fibrous cap having small round cells near the surface and foam cells at the cap-necrosis boundary, *4)* necrotic core with crystalline cholesterol, *5)* atherophagocytosis at the base-necrosis boundary, *6)* small round cells in the deepest part of the fibrous base, *7)* medial erosion, *8)* adventitial infiltrate by small round cells. H&E, ×50


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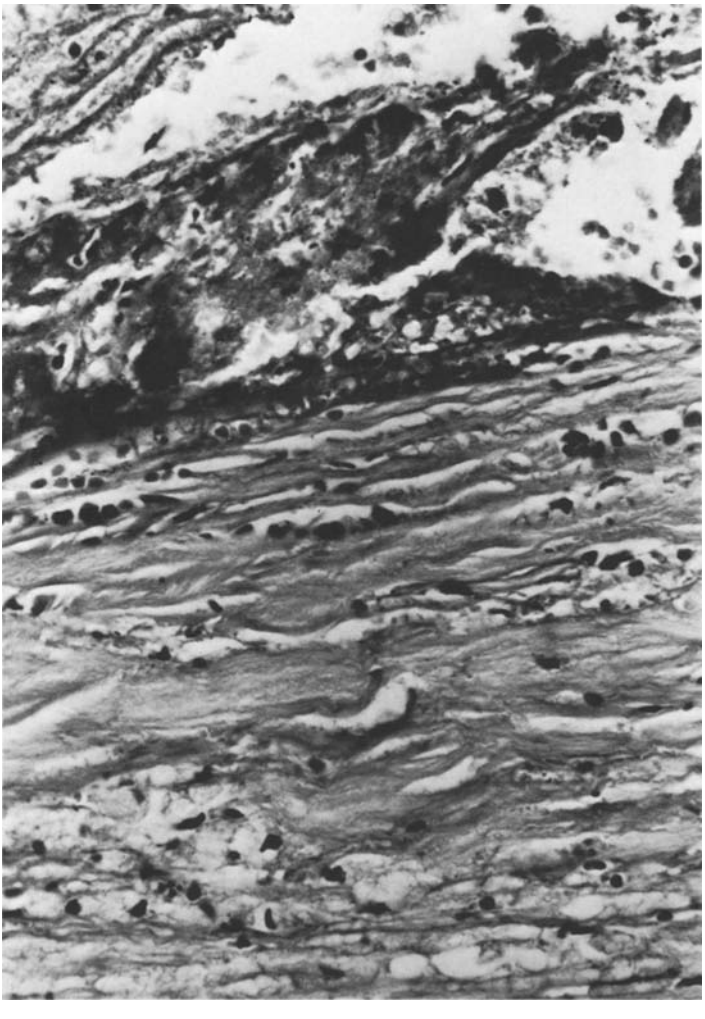

Fig. 2. Enlargement of regions 2&3 from Fig. 1 showing small dark round nuclei beneath the thrombus and foam cells below these. H&E, ×200

narrowings with myocardial scar (arteriosclerotic occlusion). During the 18 month period that the cases were being collected, 35 cases with thrombus and 28 with arteriosclerotic occlusion were encountered in men and women under age 65. The breakdown of these by age and sex is given in Table 1 along with similar data from a previous, similarly composed series. For men and women in both series of cases, the proportion of cases having thrombosis was highest under age 45 and lowest over age 54. Too few women are included to comment upon sex comparisons. The number of men is ample to declare the age differences statistically significant. In some cases, collection of adequate samples was not logistically practical because of other activities in the morgue at the time. The cases that escaped collection

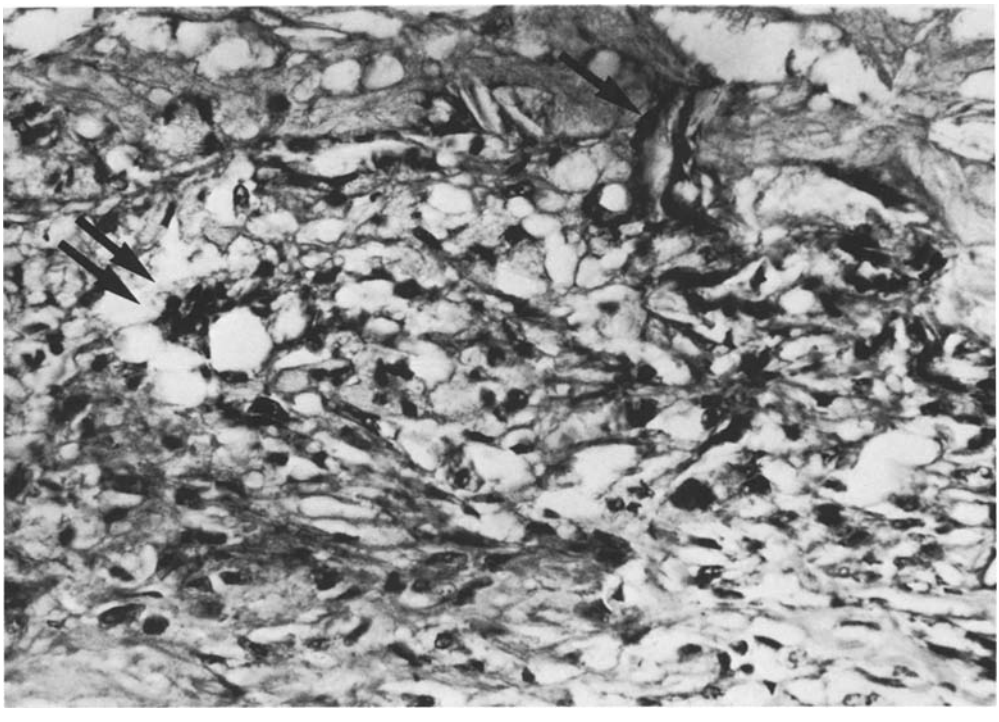

Fig. 3. Enlargement of region 5 showing atherophagocytosis at the base-necrosis boundary. Phagocytized cholesterol (*arrow*) and a multinucleate giant cell (*double arrow*) are noted. H&E, × 200

were not known to differ from the available ones except for the inconvenient time of their occurrence. Some examples of thrombosis were used in preliminary hypothesis formation (Tracy 1984), and these were excluded here. This yielded a usable sample of 18 thrombosis and 23 arteriosclerotic occlusion deaths to examine microscopically.

Kinds of fibrous plaques. Most fibrous intimal thickenings lack a necrotic core; this kind was never seen under a thrombus. Along with a necrotic core the typical thrombogenic plaque was characterized by densely packed, large and numerous foam cells within the loose and fragile connective tissue of the fibrous cap. The cap was very often ruptured (81%) with mixing of blood, foam cells and plaque gruel to form thrombus (Table 2). An example of a plaque, typically thrombogenic except without rupture, is in Fig. 1. The cap often had superficial dense collections of mixed cell types including polys, plasma cells, capillary endothelium and small cells resembling lymphocytes (72%) (Fig. 2). At the boundary between the necrotic core and the fibrous base of the plaque, a large population of cells was often seen with features suggesting phagocytic activity (75%) (Fig. 3). These cells differ appreciably from the foam cells in the cap. Rather than foamy

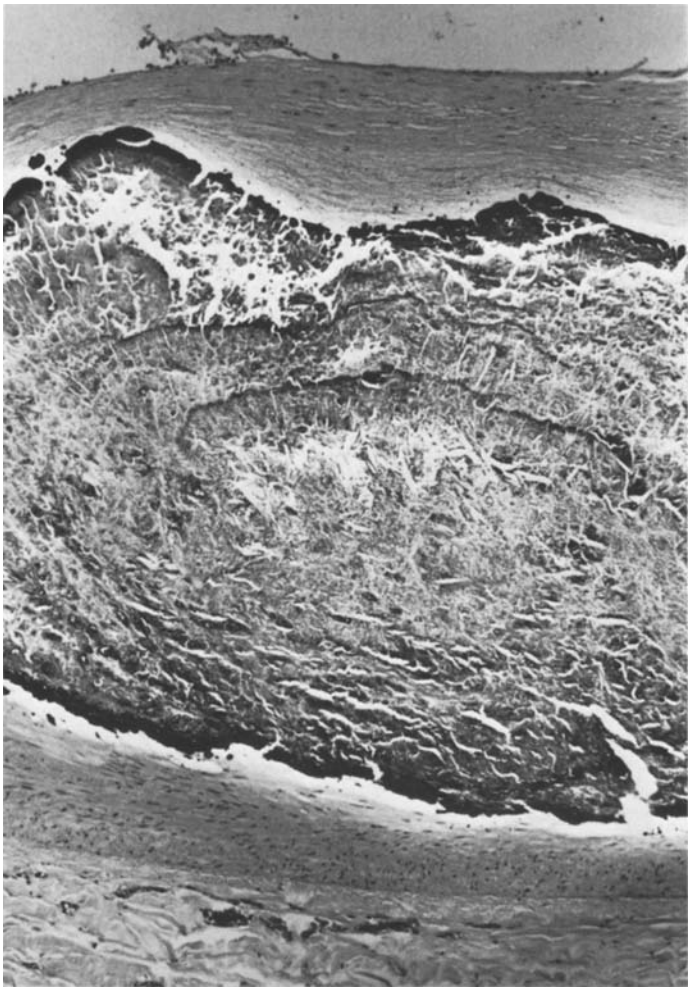

Fig. 4. A typical arteriosclerotic occlusion in a case of coronary heart disease death without thrombosis. The necrotic core is calcified, trapping crystals of cholesterol in the mineral matrix. Features 1–3 and 5–8 are absent. H&E, × 50

cytoplasm, they have compact amphophillic cytoplasm. They are often spread thinly over the surface of cholesterol crystals, apparently surrounding and engulfing the crystals, seeming to merge into a syncytium when doing this. Foreign body giant cells are also sometimes seen in this phagocytic core-base boundary. Also within the fibrous base at its deepest boundary, are dense collections of mixed cell types chiefly resembling lymphocytes or undifferentiated mesenchymal cells (94%). These cells can sometimes be seen in a simplified remnant of media or at other times merging with adventitial infiltrates through a wholly eroded media. The adventitia is often infiltrated by cells of an apparently inflammatory nature (75%).

Another kind of plaque is seen in cases with widespread calcific coronary narrowing and cardiac scars (Fig. 4). In these plaques the necrotic core

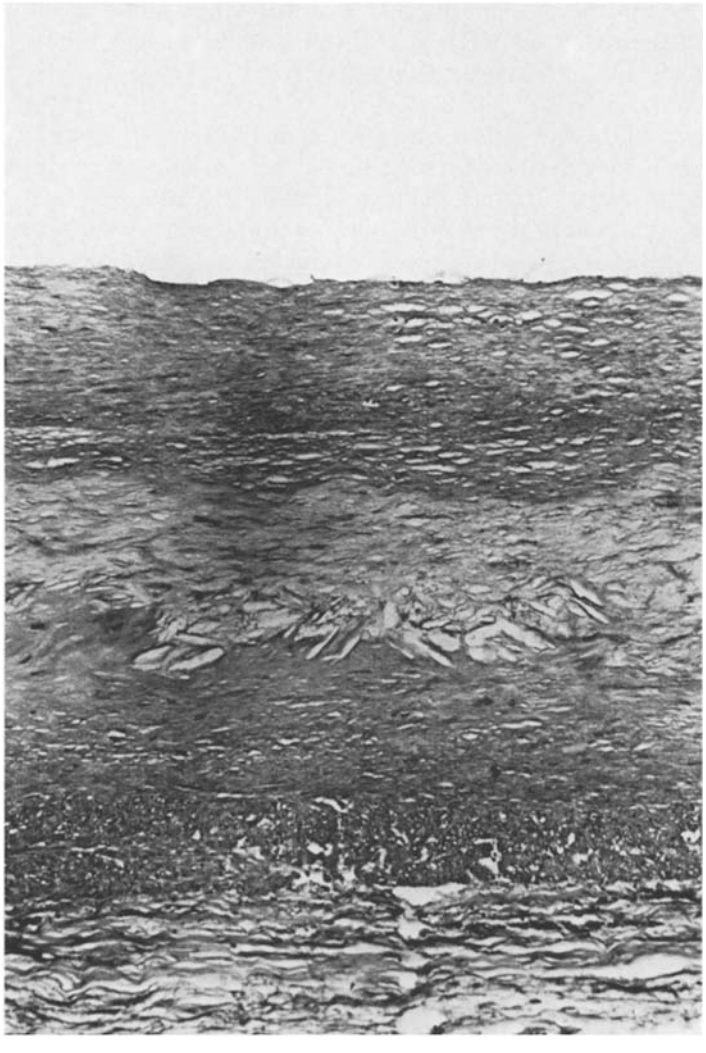

Fig. 5. A typical "innocuous", "quiescent", "inert" coronary plaque from someone without heart disease. Crystals of cholesterol in the necrotic core at the base-necrosis boundary are larger than those in Fig. 1. Features 1–3 and 5–8 are absent. H&E, × 50

is densely calcified, trapping crystalline cholesterol in a mineral matrix. Calcification also commonly affects non-necrotic cap and base and non-necrotic intimal thickenings. In the absence of thrombus these plaques seldom have any of the typical thrombogenic features (6–28%), as if the calcification somehow halts these cellular activities. Nevertheless, where thrombosis is present these plaques usually also contain these features (73–91%, Table 2).

In control cases having no heart disease, the nine thrombogenic features examined are usually absent in the apparently "innocuous" necrotic

plaques. These innocuous plaques have cholesterol in crystals that generally seem larger than those in the thrombotic plaques, and that seem "inert" because of the lack of cellular reactions to them (Fig. 5).

Quantitative findings. All of the features illustrated in the typical thrombogenic plaque of Fig. 1 were frequently seen in the 32 thrombotic plaques of this study. This was true in the 21 plaques identified as cause of death on gross inspection and in the 11 thrombotic plaques found during microscopy in 8 of the cases having arteriosclerotic occlusion as cause of death (Table 2). However, some of these features were also commonplace in the innocuous plaques of cases having no heart disease and in the quiescent plaques of advanced arteriosclerotic occlusion without thrombosis. Taking the presence of each feature as a percentage of examined plaques, the differences of these percentages between thrombogenic and innocuous plaques reflects the degree to which the respective features reflect thrombogenicity. For example, consider the deep cellular infiltrates occurring in the fibrous base of the plaque where it abuts the media or the adventitia in the absence of the media. Such infiltrates were judged to be present in 94% of the 32 thrombotic plaques, but only 24% of the 94 innocuous plaques (Table 3). The difference between the percentages, $94-24=70\%$ units, is a measure of thrombogenicity as reflected by deep cellularity. The foci of foam cells were prevalent in thrombotic plaques (88%), but were also frequent in innocuous plaques (53%), and only $88-53=35\%$ percentage units separate the groups. Deep cellularity is in these data much more specific to thrombogenicity than is foam cell infiltration. By these measures of thrombogenicity, the best differentiators were plaque rupture and hemorrhage (76 and 77% units respectively) (Table 3). Other features of high valuation were adventitial infiltration (49), superficial cellularity (50), phagocytosis (57) and deep cellularity (70), all features usually referred to as "inflammatory". Foam cells and medial erosion were of less value (35 and 31 units respectively). Calcification was antidiscriminatory (-12 units), probably because thrombi occurred in younger subjects.

Discussion

Most authors classify their cases of coronary heart disease as those with thrombosis or those with arteriosclerotic occlusion. Some of the authors tabulated the breakdown by age (Adelson and Hoffman 1961; Crawford et al. 1961; Newman et al. 1982; Spain and Bradess 1960; Tracy 1983; Yater et al. 1948). The age groupings were not identical in those studies, and for the combining of the studies into a total, the 10-year, 15-year and 20-year groups were divided into 5-year groups rather like a sliding average (Table 4). In 4 of 5 studies comparing age groups, and in the total of all studies, the frequency of thrombosis was highest in the young and lowest in the old. The sole exception is the report of Spain and Bradess (1960). The reason for this discrepancy is likely to be the criteria for diagnosis. To avoid accepting false positives into the series of CHD cases, strict criteria

Table 4. Number of cases of death due to coronary heart disease (No.) and percent having coronary thrombus (%Thr.) by age as given in six reports[a]

Age	Yater		Adelson		Spain		Crawford		Tracy		Newman		Total	
	No.	%Thr.	No.	%Thr.	No.	%Thr.	No.	%Thr.	No.	%Thr.	No.	%Thr.	No.	%Thr.
<24	25	68	4	50									46	52
25–29	59	49			54	13	25	72					99	50
30–34	95	54	60	40							74	72	171	59
35–39	74	57							25	88			151	60
40–44			174	39	139	25	25	60					195	49
45–49									42	67			185	49
50–54			137	29	148	25	25	32					176	31
55–59									55	44			183	30
60–64			88	26	109	34							126	33
65–69													98	29
70–79			34	21	35	25							52	23
80–89			3	0									20	20

[a] Because age groupings differ among studies, the total estimates require that the cases expressed by 10-year and 20-year groupings must distributed among the constituent 5-year intervals for the summation over all studies

for confident anatomic diagnosis were generally observed in most studies. Spain and Bradess (1970) were concerned with avoiding false negatives (exclusion of true CHD cases), and therefore used minimal criteria for designating CHD as cause of death. The category of subjects (nearly all of them young men) included as CHD by some pathologists and excluded by others constitutes an especially interesting group. Yater et al. (1948) say, "In forty-six patients the arteries showed neither sclerotic nor thrombotic occlusion but only thickening of the walls and narrowing of the lumina. It is quite possible that a diligent search might have uncovered more severe lesions, since these were unquestionably patients in whom death was the result of coronary artery disease, proved by clinical observations and by absence of any other adequate cause of death..." No case of this kind was accepted into the study reported here.

The findings in this study of a high percentage of thrombosis in young CHD cases may or may not eventually be verified. Either way, the plaques in thrombotic cases came from younger subjects than did plaques from cases of arteriosclerotic occlusions. The plaque features identified as reflecting thrombogenicity may therefore also reflect youth or an earlier stage preceding arteriosclerotic occlusion. Those persons who survive the first few thrombotic events might be expected at a later age to reveal coronary plaques in formerly thrombotic places and myocardial scars in formerly infarcted places. If this sequence is characteristic of all or most CHD subjects, then the nine thrombogenic plaque features examined (Fig. 1) must be transient, coming and going along with the thrombus.

Many of the features of thrombogenic plaques have a close resemblance to arterial wall reactions that follow thrombosis (Filshie and Scott 1958).

The possibility that thrombosis precedes and causes those features seems unlikely for three principal reasons. First, the thrombus usually concides with plaque rupture, an acutely fatal event often accompanied by myocardial necrosis of less than 24 h duration. Second, in the absence of easily demonstrable plaque rupture, thrombus is small and fresh, being composed of fibrin and platelets arranged in a manner characteristic of clots recently formed in a moving blood stream (O'Brien 1958). Third, plaques elsewhere in the coronaries away from the site of thrombosis also have high frequency of thrombogenic features, 41 to 60% compared with 18 to 26% in control cases (Table 3). This third finding suggests that thrombogenicity is a general characteristic of plaques within that individual. Thrombosis might therefore be an accident befalling one or more of the most irritated plaques as the thrombogenicity comes and goes episodically. Alternatively, it might be the inevitable terminus in the young subject with the most fulminant course of the disease.

On the other hand, evidence is easily found in some plaques to indicate that the current thrombotic event happened upon a site of organizing former thrombus (Chandler et al. 1974). We found three such cases in our preliminary series, although none in the 18 cases reported here. Perhaps the nine thrombogenic features might be residual from a thrombus so fully organized as to obliterate all other evidence of its origin.

The plaque features which best discriminated thrombogenicity, aside from the terminal plaque rupture and hemorrhage, were various kinds of hypercellularity usually called inflammatory. Erosion of the media and fibrous cap leading to plaque rupture by an expanding necrotic core therefore seems in some way associated with influx of small round cells and phagocytes. That these cells may be monocytes evolving into foam cells and phagocytes merits consideration. Small cells deep in the fibrous base of the plaque are often associated with medial erosion and plaque bulging into epicardial fat. These cells may be undifferentiated mesenchymal cells busy remodeling the artery wall. By electron microscopy, Stary (1978) has documented the absence of such cellular activities in nonthrombotic plaques.

On the assumption that the small cell infiltrates of thrombotic plaques are inflammatory, a number of etiologies for these have been proposed. Bacteria or bacterial toxins from a remote focus of infection (Boyd 1928; Klotz 1910; Saphir 1955; Schwartz and Mitchell 1962; Zak et al. 1952), viruses or viral antigens (Melnick et al. 1983), rheumatic fever (Schwartz and Mitchell 1962), autoimmunity and antigen-antibody complexes (Parums and Mitchinson 1981), hypertension (Klotz 1910), and ruptured or leaky vasa vasorum (Chapman 1969) have all been described in the human and most have been shown experimentally to cause inflamed intimal lesions.

Knowing that thrombosis favors regions of severe focal narrowing (Chapman 1965; Crawford et al. 1961; Falk 1983; Roberts and Buja 1972), vibrational energy of turbid flow could be proposed as an irritant which might over time produce the spectrum seen in Fig. 1 (Texon 1957).

Two fundamental facts dominate the findings of this study, and these have been repeatedly described (Branwood and Montgomery 1956; Chap-

man 1965; Constantinides 1966; Friedman 1971; Tracy 1984). Under a thrombus the plaque always has a necrotic core, but necrotic cores are also easily found in the commonplace "inert", "quiescent", "innocuous" plaques. As noted by Branwood and Montgomery (1956), "Attention may be directed also, however, to the fact that though in many examples the fatty material appears to have been inert, in others there is intense round-cell infiltration with giant cells in relation to the fat. Is this to be interpreted as a reaction to fats which are particularly irritant, or is it a demonstration of unusual response on the part of the individual?". "The bulk components of the atheronecrotic material, cholesterol, cholesterol-ester, phospholipid, must have been themselves innocuous within the innocuous plaque...some unidentified trace or minor component may be the noxious one." (Tracy 1984). The oxidation products of cholesterol studied by Taylor et al. (1979) could be one class of such lipophillic noxious substances. Perhaps the foam cells in the fibrous cap and the phagocytes in the fibrous base are reacting to these trace or minor components, cleansing the plaque gruel to leave the purified cholesterol in the inert form of large crystals.

Most of the man-made chemicals that pollute the environment of industrial societies are lipid soluble. The necrotic core of an atherosclerotic plaque is a stationary mass rich in oily materials. Hence, man-made pollutants could be expected to partition into the oily phase of the plaque core out of the aqueous phase of the blood. The fact that blood proteins are avid lipid carriers might promote the process by first drawing the chemicals into the blood from the lungs, intestine and skin and later delivering them to the plaque. Such a delivery sytem could, in theory, convey a large variety of highly toxic substances into what amounts to a lipid "sink", where the poisoning of foam cells might block secretion of cholesterol onto high density lipoprotein (Mahley 1983), and cause the death of foam cells to add substances to the necrotic core (Stary 1978). The tarry polycyclic compounds from the smoke of tobacco, oil and coal products would be of special concern, because a steric resemblance to cholesterol might cause them to cocrystallize with the abundant plaque constituent, and to interfere with its metabolic functions. How many decades or centuries of industrialization might be required to saturate the environment of a whole population with such toxic lipophillic pollutants might be hard to determine. The close relationship of coronary heart disease to industrialization and tobacco use does, however, make this hypothesis intriguing.

Conclusions

Atherosclerotic plaques usually exist innocuously in the coronary arteries of most middle and old aged people. What causes a quiescent plaque to undergo thrombosis is an unsettled question. Certain morphological features have been suggested to hold an ominous meaning when seen in coronary plaques. These features are dense nodular infiltrates of foam cells and diffuse small cell infiltration of the fibrous cap over the necrotic core, adventitial and plaque base infiltration by small cells that merge through destruction

of the media, and a newly described appearance at the necrosis-base boundary interpreted as atherophagocytosis. A test of the thrombogenetic propensity of these plaque features would involve a systematic comparison between thrombotic and quiescent plaques in a sufficient number and variety of cases. This feasibility study of 18 cases of coronary thrombosis and various comparison cases has tentatively suggested that large differences between the two kinds of plaque can be demonstrated by practical methods.

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