CLINICAL PROGRESS

Atheromatous Embolism

By Robert S. Eliot, M.D., Vladimir I. Kanjuh, M.D.,
and Jesse E. Edwards, M.D.

EMBOLISM of atheromatous material may originate either in the ulcerated atheromatous aorta or arteries. When the aorta is the primary source for embolism of atheromatous material, one of two disease states may develop, depending upon the size of the embolus. If there is a single large embolus, a major clinical event usually results. If, on the other hand, there are multiple small emboli, usually more than one organ is involved by embolic arterial occlusion. Multiple system involvement may simulate periarteritis nodosa or bacterial endocarditis. If emboli are concentrated in one organ, the clinical picture may suggest severe primary disease of that organ while, in fact, it may be secondary to primary involvement of the aorta. Often, when nonvital structures are involved, atheromatous embolism is subclinical.

The purpose of this report is to review the literature on the subject of arterial occlusion resulting from embolism of atheromatous material originating predominantly in the aorta. For purposes of orientating the reader, a description will first be made of the essential pathologic findings and the historical background of embolism of atheromatous material.

When emboli arise from a branch of the aorta, occlusive effects are confined to the organ supplied. Therefore, emphasis will be placed upon atheromatous embolism as it pertains to the various organs. In addition to atheromatous embolism, thrombotic and calcific material may be dislodged from the ulcerative atheromatous aorta. This phenomenon, however, will not be a part of this review.

Pathologic Anatomy and Historical Background

Panum,[1] in 1862, was, so far as we are aware, the first to mention the phenomenon of atheromatous embolism. He quoted the necropsy findings of Dahleruf and Fenger in a case in which the entire process was confined to the coronary arterial system. The patient, the famous Danish sculptor, Thorwaldsen, died suddenly while attending the theatre in Copenhagen. In "the" coronary artery they demonstrated a ruptured atheroma. Distal to this, the lumen of "the" coronary artery was filled with soft atheromatous material. They considered that the material occluding the vessel distally had originated by a process of embolism from the proximal ulcerated lesion.

Atheromatous embolism occurs in two principal forms. The first form results from dislodgment of one or several major atheromatous plaques, including contained cholesterol crystals. The material dislodged is often of sufficient size as to occlude a major systemic artery, including a coronary artery. Clinically, lodgment of such an embolus results in major dysfunction of the affected organ.

The second form of atheromatous embolism results from the ulceration of plaques, permitting the release of cholesterol crystals and other atheromatous components from the plaque. The resulting emboli are composed

principally of cholesterol crystals and lesser amounts of other atheromatous material.

In order to distinguish the two major forms of atheromatous embolism, the larger emboli will be called atheroemboli, whereas the smaller emboli, high in crystalline content, will be referred to as cholesterol emboli.

In cholesterol embolism, the particles are smaller and more numerous than in the first form. Small arteries, frequently with diameters from 150 to 200 μ, are usually involved.

Further, the technic of histologic examination must take into account the chemical peculiarities of cholesterol. When the usual methods for preparing histologic sections are employed, cholesterol is dissolved leaving the characteristic spaces that had been occupied by the crystals. In the preparation of sections for specific identification, fixatives that do not dissolve cholesterol and then specific stains for cholesterol must be used. After frozen section, the Schultz test stains the acicular, doubly refractile cholesterol crystals green in a few minutes and brown in 30 minutes. Also, it is possible to use polarized light on frozen preparations to show the birefringent character of the cholesterol crystals.

Classically, cholesterol embolism involves multiple vessels in several organs. Many emboli go unrecognized because the vessels are small and collateral circulation prevents infarction. When clinical signs are caused by cholesterol embolism, the picture is usually that of chronic disease characterized by involvement of more than one organ. The focus of this review will be directed toward cholesterol embolic phenomena, since, clinically, this form of embolism leads to less distinctive features than does atheroembolism.

In review of the reports in the literature, it was not always possible to distinguish cholesterol embolism from atheroembolism. Where this distinction was possible, it will be made; elsewhere the general term, atheromatous embolism, will be employed.

The aorta almost invariably shows extensive involvement, at least of the abdominal portion, by an ulcerative atheromatous process. Consequently, the abdominal viscera are most
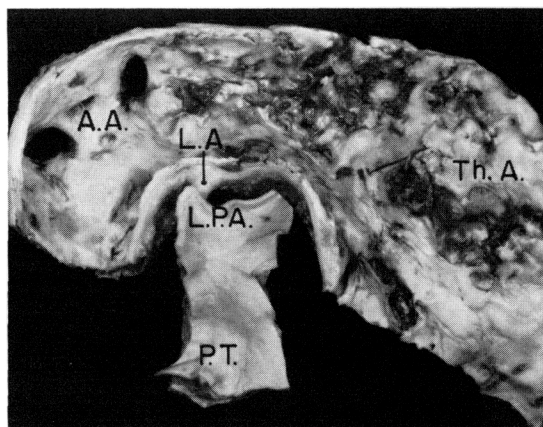

Figure 1

Interior of aortic arch (A.A.), thoracic aorta (Th. A.), and pulmonary trunk (P.T.) demonstrating severe ulcerative atheromatous involvement of the aorta. The severity of the ulcerative process of the aorta is contrasted with the normal intimal surface of the pulmonary trunk (P.T.) and left pulmonary artery (L.P.A.). L.A., ligamentum arteriosum.

frequently involved by atheromatous emboli. In some cases, particularly those associated with syphilis or gout,[2] the entire thoracic aorta also may be severely involved with a process of ulcerative atherosclerosis (fig. 1).

Histologically, in the aorta, many of the atheromatous lesions contain considerable amorphous eosinophilic material, lipophages, and cholesterol crystals (fig. 2). The emboli in small arteries are composed of this material (fig. 3).

When cholesterol crystals are predominant in small arteries, it may be assumed that smaller amorphous particles of atheromatous material have passed downstream beyond the site of impaction of the crystals. Additionally, amorphous particles may become phagocytized. Because of the larger size and needle-like shape of cholesterol crystals, they, in contrast to other atheromatous material, may lodge in an arterial lumen and damage the layers of the arterial wall.

Several factors may operate to cause dislodgment of atheromatous material from the diseased aorta. One of these is hemorrhage into atheromas of the aorta. This may be followed by rupture of the overlying con-
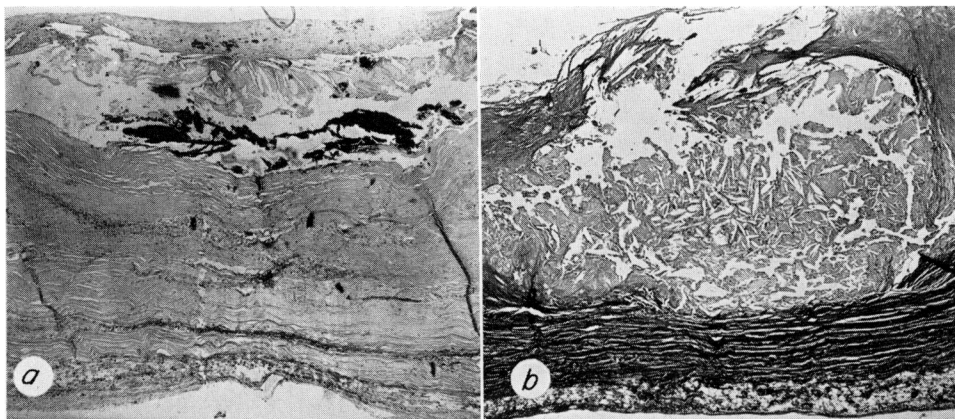
Figure 2

Photomicrographs of the aortic wall demonstrating syphilitic aortitis and severe ulcerative atheromatous lesions. a. Syphilitic lymphoplasmocytic infiltration of the adventitia and media with replacement of elastic fibers of the media by connective tissue. Large ruptured atheroma with cholesterol crystals and calcific deposits. Hematoxylin and eosin; × 35. b. Large ruptured atheroma containing cholesterol crystals. Elastic tissue stain; × 35.

nective tissue and extrusion of atheromatous material into the aortic lumen.

The dislodgment of atheromatous material from the aorta is spontaneous in some circumstances. At other times, it may follow sudden activity such as coughing, tenesmus, or lifting. Occasionally, also, it is associated with surgical manipulation of an aortic aneurysm.[3]

Meyer's [4] description of cholesterol embolism and the associated reactions in the ar-

Figure 3

Photomicrograph of kidney. Small artery obstructed by impacted and encased cholesterol crystals. Hematoxylin and eosin; × 80.

terial wall is classic. The lodgment of the emboli that are composed predominantly of cholesterol crystals occurs commonly in vessels ranging from 150 to 200 μ. This is followed by a peculiar form of arteritis with infiltration of giant cells ("arteriitis obliterans" or "Riesenzellarteriitis"). Then follows the stage of encasement of the cholesterol crystals by giant cells. Later, the giant cells tend to disappear, leaving the cholesterol crystals encased by connective tissue. The entire process of embolism and reaction results in obliteration of the lumen. The presence of eosinophils in the inflammatory stage has been described by several authors. Sturgill and Netsky[5] mentioned the possibility that cholesterol crystals mechanically penetrate all layers of the arterial wall. Subsequently, organization occurs, not only in the arterial lumen, but also in the arterial media and adventitia.

In 1945 Flory[6] wrote a classic paper that seemed to stimulate considerable interest in embolism of atheromatous material from the aorta. Among 267 consecutive necropsies, he observed nine instances in which embolism of atheromatous material from the aorta had occurred. Following the appearance of Flory's report, numerous cases were described in
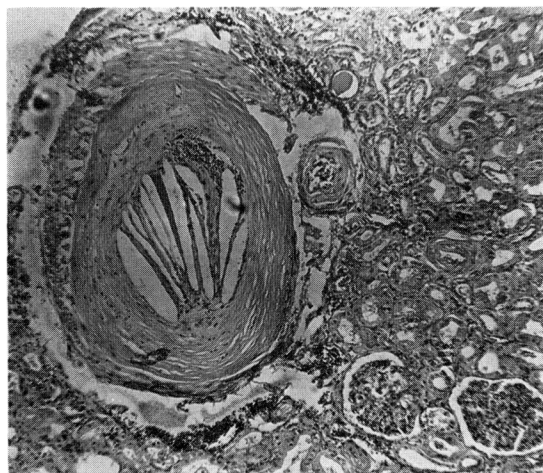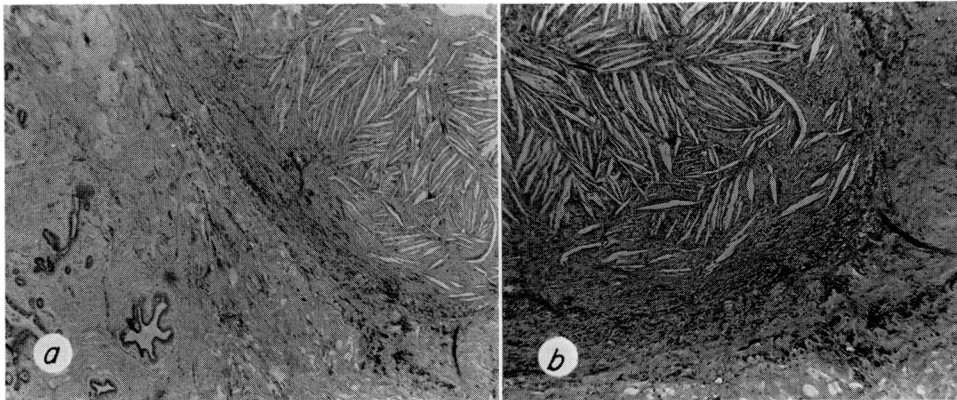
Figure 4

Photomicrographs of a cholesterol granuloma at the site of previous hemorrhage in a breast involved by fibrocystic disease. a. In the lower left aspect of the illustration are glands and fibrous proliferation representing fibrocystic disease of the breast. At the upper right are cholesterol crystals surrounded by a capsule of connective tissue in which a large amount of hemosiderin is present. Hematoxylin and eosin; × 35. b. Close-up view of the cholesterol granuloma seen in a demonstrating the cholesterol crystals, surrounding granulomatous connective tissue reaction, and hemosiderin. Hematoxylin and eosin; × 75.

which embolism of atheromatous material was identified at necropsy.[7–11]

Flory[6] attempted to reproduce cholesterol embolism in animals. He injected cholesterol suspensions into the ear veins of rabbits and sacrificed them after 1 and 7 days. He reported that he was able to identify in the pulmonary vessels crystals like those involved in human cholesterol embolism.

Snyder and Shapiro,[12] in 1961, performed an extensive investigation that amplified the observations of Flory[6] and Meyer.[4] Suspensions of cholesterol crystals were injected into the ear veins of 16 rabbits. At intervals up to 160 days after injection, histologic examination of the lungs was made. By this technic, the authors were able to pinpoint the evolution as well as the duration of the histologic changes.

Three days following injection, panarteritis with eosinophilic infiltration and hyperplasia of the intima was demonstrated. Giant cells were present near the crystals and leukocytes were found in the adventitia. Six days after injection, intimal fibrosis and sequestration of the crystals by foreign-body giant cells were the major histologic findings. These changes persisted without further develop-

ment for 160 days, when the experiment was discontinued. They concluded that cholesterol crystals acted as a "permanent" foreign body. This confirmed the hypothesis of Meyer[4] that cholesterol crystals are not soluble in body fluids or removable by phagocytosis.

Snyder and Shapiro[12] also studied the development of peripheral gangrene in nine dogs by injecting cholesterol suspensions into the femoral artery. Three of the dogs developed gangrene; in them thrombosis had occurred at the sites of lodgment of cholesterol emboli. They concluded that the ischemic effects of cholesterol embolism are compounded by the tendency for impacted cholesterol to cause thrombosis.

The presence of cholesterol crystals in the lumina of small arteries is usually regarded a result of embolism. Others, however, have suggested that it represents an expression of atherosclerosis or transformation from previous local thrombosis.

The theory of embolism is supported by the constant presence, in cases of so-called cholesterol embolism, of ulcerative aortic atherosclerosis. Additionally, the material at both locations is the same, histologically. Furthermore, the involved arteries are smaller than

those usually found to have atherosclerosis in situ. Instances are also found of cholesterol crystals in the arterial lumen, without attachment to the arterial wall, which, in turn, is normal.

The idea of transformation of thrombi into cholesterol crystals in situ is supported by the production of cholesterol by hemolysis. Also, it has been thought that local hemorrhage may give rise to cholesterol deposits.

Sesenna,[13] observing accumulations of cholesterol crystals in goiterous thyroid glands, explained the presence of the crystals as originating in areas of hemorrhage. We have observed cholesterol crystalline deposits in the breast in a case of fibrocystic disease with evidence of antecedent hemorrhage (fig. 4).

While the latter observations may be used in support of thrombotic origin of intra-arterial cholesterol crystals, it is to be emphasized that there are strong arguments against this hypothesis. For instance, although thrombosis occurs more commonly in veins than in arteries, cholesterol crystals are seen only in arterial vessels. Moreover, cases of arterial thrombosis far exceed cases with cholesterol crystals in arterial lumina.

Organs Involved

Atheromatous embolism should be considered in the individual with disease of sudden onset involving one organ or multiple organs. In gout and syphilitic aortitis, which are frequently associated with extensive ulcerative aortic atherosclerosis, atheromatous embolism appears to be more common than in other states. Diabetes mellitus, with its predisposition to atherosclerosis, is not uncommonly an associated condition in individuals having atheromatous embolism.

Organs representing sites of predilection for lodgment of atheromatous emboli are the kidney, spleen, and pancreas, in decreasing order of frequency.[14] Among other frequent sites that have been identified as receiving atheromatous emboli are the heart, brain, small intestine, skin, and lower extremities.

Coronary Arteries

In 1896 Oestreich[15] and in 1897 Chiari[16]

described emboli in the left coronary artery from atheromatous aortae with superimposed thrombosis. Hektoen[17] and LeCount[18] added other instances.

Wenger and Bauer[19] reviewed the literature on coronary embolism in general. They concluded that approximately 4 per cent of episodes of coronary embolism result from dislodgment of cholesterol in aortic atherosclerosis. Several other authors have also mentioned the frequent finding of atheromatous material in the coronary arterial system secondary to embolism from the atheromatous aorta.[20, 21]

In 1940 Porter and Vaughan[22] and in 1943 Pratt-Thomas[23] emphasized the predisposition to atheromatous coronary embolism in syphilitic aortitis. It is of interest to attempt explanation for this peculiar association.

In the first place, the aorta with syphilitic medial involvement commonly also exhibits extensive ulcerative atherosclerosis. The extensive atheromatous involvement of the proximal part of the aorta would, of itself, represent a strong underlying factor for embolism to the coronary arteries. The aortic valvular insufficiency, which commonly occurs in syphilitic aortitis, would introduce a to-and-fro element in the direction of blood flow in the ascending aorta. The turbulence so created may serve to dislodge more foreign material from the diseased aortic intima than would normal blood flow. The reversed flow would also increase the chances of retrograde coronary embolism.

As mentioned, the source of atheromatous emboli in a coronary artery may be an atheroma in a proximal segment of the involved coronary artery.[1, 24]

When cholesterol embolism is directed into the coronary arteries, ischemic changes may involve sufficiently small areas as to be subclinical, although electrocardiographic abnormalities of the T waves may be observed in some cases.

In syphilitic aortitis, angina and abnormalities of the T waves may be interpreted simply as two manifestations of aortic incompetence. On the other hand, the frequent occurrence

of cholesterol embolism in individuals with syphilitic aortitis should alert the clinician to the possibility of atheromatous coronary embolism.

When atheromatous embolism is responsible for sudden, unexpected death or acute transmural infarction, it is usually the result of a large atheroembolus rather than the smaller cholesterol form. One may postulate that thrombus formation occurs at the site of cholesterol embolism to a coronary artery in a manner similar to that described experimentally.[12]

Brain

Fisher [25] in 1951 reported that cerebral embolism from atheromatous plaques is a cause of repetitive "small strokes." Later Winter [26] and Kaplan and associates [27] described instances of multiple cerebral infarcts associated with atheromatous emboli from the aortic arch or carotid arteries. Witmer and Schmid,[28] described a case of a retinal cholesterol embolism.

In 1963, Sturgill and Netsky [5] described the case of a normotensive patient with multiple small cerebral and cerebellar infarcts in which cholesterol crystals were present in those leptomeningeal arteries adjacent to the areas of infarction. Emboli were found in other organs, as well. The source for embolism was the aorta, which displayed erosive atheromatosis in its abdominal portion and "friable atheromatous material" at the origin of arteries arising from the arch. The peripheral blood in this case contained 7 per cent eosinophils. The authors also reviewed 13 similar reported cases of cerebral infarction.

Gastrointestinal Tract

Gore and Collins [10] reported four instances of occlusion by atheromatous emboli of submucosal arteries in the intestinal tract. Ulcerations of the jejunum overlying these lesions were seen in one case, whereas nonulcerative lesions of the colon were observed in the remaining three cases. Embolic lesions of atheromatous material involving the small bowel or stomach,[4, 7, 26, 29] the large bow-

el,[2, 7, 8, 10] and gall bladder and common bile duct,[7, 8, 30] have been reported. Gastrointestinal bleeding may result from atheromatous embolic phenomena. Acute pancreatitis, of varying degrees of severity, was considered to be the result of embolic process.[14, 30] The severity of the pancreatitis, clinically, was directly related to the number of vessels involved.[30]

Kidney

An interesting complication of atheromatous embolism is the frequent association with progressive and unremitting systemic hypertension. Handler [8] in 1956 indicated that in 15 of 20 cases of atheromatous embolism there was involvement of renal arteries with hypertension or cardiac hypertrophy. In four of the 20 cases, syphilitic aortitis was present. Later, Margolin and associates [31] and Thurlbeck and Castleman [3] reiterated the frequency of unilateral as well as bilateral renal involvement in atheromatous embolism and the frequency with which hypertension is associated (17 of 22 cases).

Renal failure is another serious complication of atheromatous embolism, usually as the result of multiple emboli involving the arteries within the substance of the kidneys.[10] Several such patients who died in chronic renal failure have been reported.[3, 24, 32]

Skin

Hoye and associates [33] first reported cutaneous arterial atheromatous embolism. Clinically, the lesions appear as raised, plaque-like, reddened elevations that resemble those seen in polyarteritis nodosa. Cutaneous lesions tend to involve the lower extremities. When these nodules are accompanied by fever, myalgia, eosinophilia, hypertension, and hematuria, it is difficult to differentiate the condition from polyarteritis nodosa.[11, 34]

Bacterial endocarditis is also a problem in differential diagnosis, when embolic phenomena of widespread distribution are present.[24]

Arteries of Extremities

Candiani [35] described two cases of cholesterol-crystal embolism to the femoral, popliteal, and tibial arteries. Both patients exhibit-

ed hypertension and extensive ulcerative atherosclerosis of both the aorta and peripheral arteries, with narrowing of the lumina of the latter. Atheromatous embolization caused occlusion of large arteries because of the pre-existent luminal narrowing.

Hoye and associates,[33] Venet and Friedfeld,[36] and Snyder and Shapiro[12] emphasized the frequency with which atheromatous embolism gives rise to gangrene of the lower extremities. These authors indicated that many instances of gangrene thought to complicate local atherosclerosis result, in fact, from embolism of atheromatous fragments that originate at sites lying proximal to the level of arterial occlusion. Their experiments in dogs also suggested that cholesterol emboli may set the stage for superimposed thrombotic occlusion.[13]

We could find no report of gangrene of the upper extremities secondary to atheromatous embolism.

Other Organs

Atheromatous emboli have been identified in the spleen, adrenal gland, thyroid gland, bone marrow, prostate, testis, liver, and in the vasa vasorum of the aorta itself.[24]

With the exception of involvement of splenic arteries, embolic occlusion in the other sites named do not usually give rise to symptoms. Symptoms of splenic involvement appear if the embolism results in infarction. Under this circumstance, pain typical of this lesion is apparent.

Summary

From ulcerated atheromatous arterial lesions, crystals of cholesterol (cholesterol embolism) or larger fragments of atheromas (atheroembolism) may be dislodged. Such emboli may originate either in the aorta or in any of the major systemic arteries and lodge in their small ramifications.

Atheromatous embolism may yield states varying from those of subclinical nature to those of obvious arterial occlusion. Myocardial ischemia or infarction, small strokes, cutaneous nodules, splenic infarction, gastrointestinal bleeding, pancreatitis, hypertension,

renal failure, and peripheral gangrene are among the clinical manifestations when arteries are occluded by emboli originating in atheromas of the aorta. Syndromes resembling polyarteritis nodosa and bacterial endocarditis may result from widespread embolism to small arteries.

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