THE EFFECTS OF ATHEROMATOUS EMBOLIZATION ON SMALL ARTERIES AND ARTERIOLES

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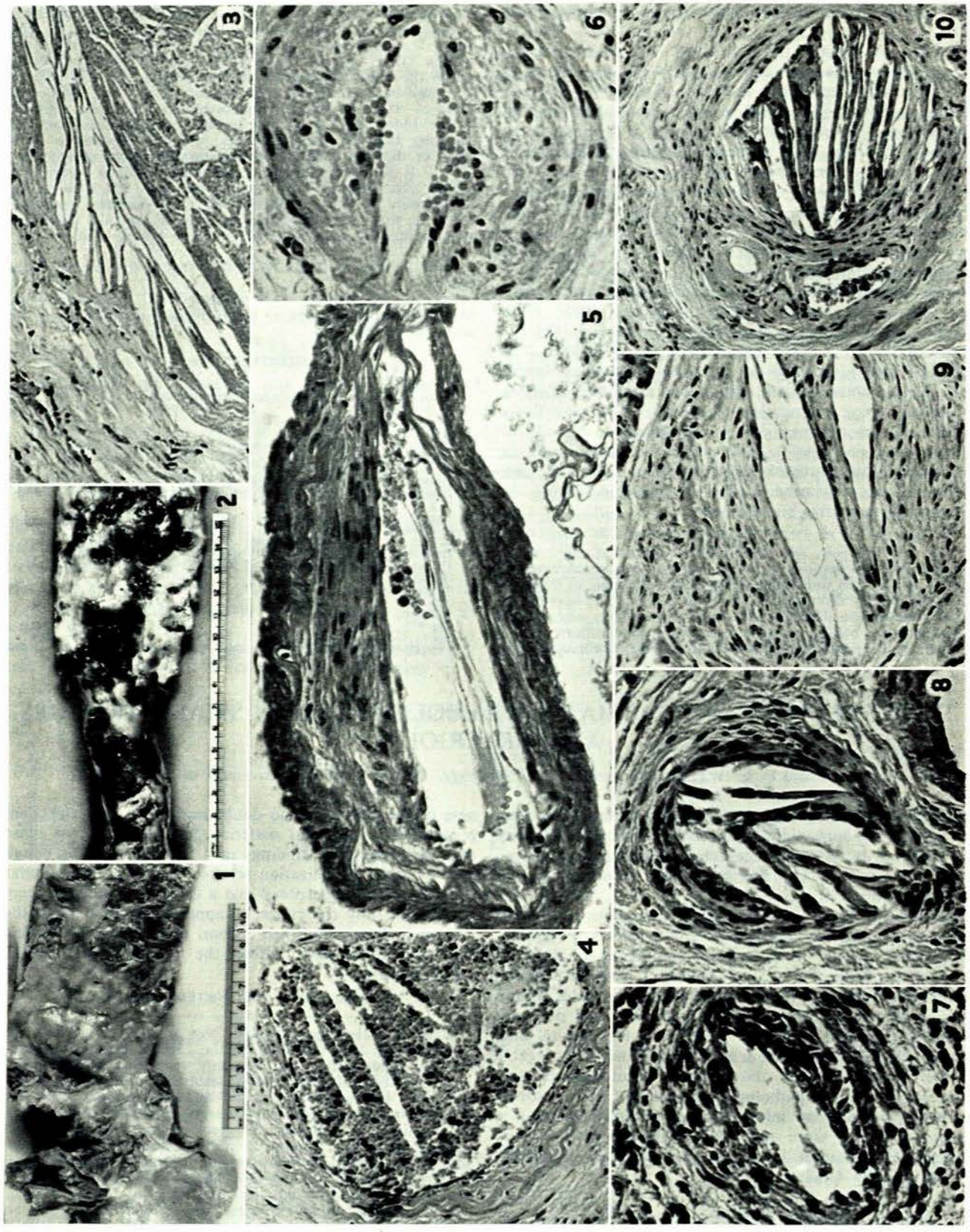
Although embolization of atheromatous material has been recognized for some time (it was first described by Panum in 1862[10]) it is only in recent years that reports of cases have appeared in the literature with some regularity, totalling over 100 cases to date. In 1945 interest was stimulated by Flory[1] who reported the findings in 9 cases of atheromatous embolization in 267 autopsies. Following this, other reports which included significant numbers of cases were those of Handler,[2] Thurlbeck and Castleman,[3] Probstein, Joshi and Blumenthal,[4] and Gore and Collins.[5] Additional reports of isolated or small numbers of cases have come from Zak and Elias,[6] Winter,[7] Sayre and Campbell,[8] Fisher, Hellstrom and Myers,[9] and Schornagel.[11] These reports covered the clinical manifestations, the vascular lesions and pathological sequelae of atheromatous embolization; and the information has been analysed in a recent review by Gore and Collins.[5] Experimental atheromatous embolization has been produced in rabbits by Flory[1] and by Otken.[12]

As the vascular lesions are unique in appearance and should not be confused with anything else, their morphology deserves greater stress, especially since a greater awareness of the entity will no doubt lead to its more frequent recognition in surgical material. It is with this in mind that we present the findings in 4 patients, in 2 of whom atheromatous embolization resulted in death. The vascular lesions were so widespread that a detailed account of them covers not only the range of appearances seen from the earliest to long-established lesions, thus adding to existing descriptions, but also outlines the natural history of the lesion as well.

CLINICAL AND POSTMORTEM FINDINGS

Case 1

A White male, aged 77 years, was admitted to hospital on 15 December 1959 and died on the 23rd of the same month. He was hypertensive and for many years had suffered from angina pectoris and dyspnoea on exertion. Three weeks before admission he had a myocardial infarct and had been confined to bed ever since on anticoagulant therapy. Three days before his final admission his level of consciousness became clouded and his general condition deteriorated. He was admitted in a confused state and appeared shocked, although his blood pressure was not low (170/110, 180/100 mm.Hg). In hospital his condition did not improve, and on the 8th day he lapsed into unconsciousness and died. On the day of death his blood urea was 250 mg. per 100 ml. The other biochemical findings were not remarkable.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At autopsy the outstanding feature was the degree of atherosclerosis of the major vessels, especially the aorta. The atheromatous plaques were discrete in the ascending aorta, but became confluent from the arch down, some showing calcification and many ulceration. The intima presented as a ragged ulcerating surface from which friable atheromatous material was easily dislodged. Fresh thrombus capped the ulcerating areas in places. The aorta was ectatic throughout its length and in the abdominal aorta there was a small aneurysm partially filled with dry laminated thrombus. The coronary vessels similarly showed pronounced atheroma with stenosis and calcification. The basilar and splenic arteries, and the renal, iliac and femoral vessels were equally affected but did not show ulceration.

The heart was hypertrophied (weight 484 G. and left ventricular thickness 2·0 cm.) and the scar of a healed myocardial infarction was present in the wall of the left ventricle; there was also a fibrinous pericarditis. The kidneys (240 G.) were reduced in size, largely owing to narrowing of the cortex, and their external surfaces were pale and coarsely granular. The spleen was slightly larger than usual (184 G.), and on section geographically-outlined areas of infarction alternated with dark, congested areas beneath the capsule. Focal areas of congestion and recent haemorrhage were noted in the mucosa of the stomach, duodenum, jejunum, ileum and colon. Small focal haemorrhages were also present in the skin of the thighs. A large area (2·0 cm.) of recent haemorrhage was present in the left cerebellar hemisphere which had tracked to the overlying meninges. No significant gross changes were noted in any of the other organs.

Case 2

This was a 65-year-old White male admitted to hospital in June 1958 in gross cardiac failure and with incipient gangrene of the toes. Peripheral pulses were not palpable in the lower limbs. Blood pressure 180/110 mm.Hg; blood urea 295 mg. per 100 ml. He had been on anticoagulant therapy for 3 months following the sudden onset of a monoplegia of the right arm, thought to be the sequel of carotid-artery thrombosis, but there was little residual weakness on his second admission. His course was steadily downhill, and he died in cardiac failure with uraemia 2 weeks after admission.

At autopsy the body was emaciated, and there was early gangrene of the 3 lateral toes of both feet. A serous effusion of 300 ml. was present in the right pleural cavity. The upper lobe of the lung on this side was covered by a fibrinous exudate and was the site of a florid confluent bronchopneumonia. Elsewhere the lungs were oedematous and showed only patchy bronchopneumonia. A healed myocardial infarct, about 3 cm. in diameter, involved two-thirds of the thickness of the posterior wall of the left ventricle, the endocardial surface being spared. The coronary vessels showed a severe degree of atheromatous narrowing, but complete occlusion was not demonstrated. The kidneys were reduced in size (combined weight 184 G.), with pale, granular surfaces. Several shallow healed infarcts, 0·5 - 1·0 cm. in diameter, were evident on the capsular surface of the atrophic spleen. The liver showed the features of chronic venous congestion.

The aorta showed a severe degree of atherosclerosis with ulceration, calcification, and medial fibrosis. It was completely occluded by pale adherent thrombus for a distance of 2 cm. above the bifurcation. The iliac arteries were filled with dry, red thrombus, which on the right extended into the femoral artery. The tortuous splenic artery was severely involved in the atherosclerotic process; the renal and basal cerebral arteries showed only isolated uncomplicated plaques.

Cases 3 and 4 were similar in many particulars to the preceding two, but differed in that the atheromatous embolization played no significant part in determining their death. They will be described more briefly.

Case 3

This patient, a 78-year-old White male, was admitted with early gangrene of the left big toe. Following surgical amputation of the toe he developed an ischiorectal abscess and septicaemia, from which he died.

At autopsy a notable degree of left ventricular hypertrophy (weight 542 G.; left ventricular thickness 1·8 cm.) suggested the presence of hypertensive disease. One of the most striking gross features was the degree of atherosclerosis involving the majority of large vessels, particularly the aorta. While the entire aorta was affected, beyond the origin of the large vessels the plaques became confluent and replaced the greater portion of the intimal surface. The majority of plaques here had undergone ulceration, discharging their lipid contents into the lumen of the aorta. The intimal surface thus had a ragged moth-eaten appearance (Fig. 1).

A large ulcerating plaque was placed in the left innominate artery, and a large plaque was also present in the right carotid artery at its bifurcation, all but occluding the lumen. At the origins of the mesenteric and renal arteries there was severe atherosclerosis but not much evidence of ulceration. Both renal arteries and the splenic artery also showed severe atherosclerosis with ulceration. In contrast to these changes the cerebral vessels showed only patchy atheroma without significant stenosis of the lumen. The right iliac artery was completely occluded by old thrombus.

The spleen (340 G.) was enlarged and the capsular surface appeared mottled. The pulp on section was very soft and autolytic, and the cut surface showed numerous red and pale infarcts beneath the capsule.

The external surfaces of both kidneys (310 G.) were coarsely granular. On section there was irregular reduction of the cortices of both kidneys and the large vessels appeared prominent and atherosclerotic. Midway along the length of the left kidney there was a large area of scarring, measuring 2 cm. in extent and resembling a healed infarct.

Case 4

The patient, a 74-year-old Coloured male, was admitted in extremis on 29 December 1961 and he died the following day. He was quite unable to supply any history, but was known to suffer from cardiac failure.

At autopsy all the organs showed signs of congestive cardiac failure. There was a notable degree of cardiac hypertrophy (weight 512 G.), largely from left ventricular hypertrophy (thickness 2·0 cm.); mild right ventricular hypertrophy was also present (thickness 0·6 cm.). Antemortem mural thrombus

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Fig. 1. Severe confluent atheroma involving the entire length of the aorta (Case 3). Extensive ulceration of plaques and discharge of the atheromatous material into the lumen have resulted in this moth-eaten appearance.

Fig. 2. Numerous confluent and ulcerating plaques of atheroma replace the intimal surface of the abdominal aorta in Case 4. Many also show overlying thrombus.

Fig. 3. Severe atherosclerosis with ulceration of the aorta (Case 2). Closely packed clefts indicate the site of the cholesterol crystals which have a pathognomonic shape and appearance. H. & E. x 189.

Fig. 4. Early atheromatous embolization in a large branch of the splenic artery. Typical clefts are lying free in the vessel lumen and are surrounded by red cells. Note absence of thrombus. H. & E. x 224.

Fig. 5. Recent atheromatous embolization in medium-sized cerebral vessel. Outlines of crystals, separated by a thin film of protein, can be seen in lumen. Eccentric proliferation of the intimal-lining cells is also present. This vessel lies in close relation to the area of cerebral softening and haemorrhage in Case 1. H. & E. x 320.

Fig. 6 Arteriole in portal tract with impacted cholesterol crystal all but occupying the lumen and compressing the media at its extremities. H & E. x 320.

Fig. 7. Two cholesterol clefts completely occupy the lumen of the arteriole in a lymph node. There is evidence of concentric intimal proliferation around the clefts. H. & E. x 384.

Fig. 8. An arteriole in the thyroid containing multiple clefts. There is intimal proliferation and migration of fibroblastic cells along the external surfaces of the clefts, completely enveloping them. H. & E. x 320.

Fig. 9. A small artery in the pancreas completely occluded by newly formed connective tissue which outlines the cholesterol clefts. Although all the indications are those of a long-standing lesion, the cholesterol crystals have apparently remained intact. H. & E. x 320.

Fig 10. A large renal artery showing the features of long-standing atheromatous embolization. Large numbers of parallel-lying cholesterol clefts, surrounded by fibroblastic cells, occupy the lumen. A significant increase of intimal fibrous tissue is associated with this. Several well-formed vessels within the lumen indicate that recanalization has also occurred. H. & E. x 189.

was present at the left ventricular apex. There was however no evidence of recent or old infarction in the myocardium.

The aorta, particularly the abdominal portion (Fig. 2), showed a striking degree of atheromatous degeneration, where many confluent plaques had ulcerated and were discharging atheromatous material into the lumen.

Apart from showing evidence of chronic venous congestion, the spleen also contained a solitary, partially-healed infarct beneath the capsule.

The kidneys were unequally reduced in size (right kidney 114 G.; left kidney 140 G.) and their external surfaces were coarsely granular owing to extensive cortical scarring. Section showed pronounced narrowing of the cortex in the region of the scars. The vessels showed a severe degree of atherosclerosis.

The pancreas was enlarged, swollen and firm. Small opaque foci of fat necrosis occurred throughout the pancreatic substance, but did not involve the adjacent peripancreatic fat. There was no evidence of haemorrhage.

A recent infarct was present in the base of the left lung.

All the autopsy evidence in this case pointed to death being due to hypertensive congestive cardiac failure.

HISTOLOGY OF VASCULAR CHANGES

All sections were stained with haematoxylin and eosin after the tissues were fixed in formalin and paraffin-embedded; in addition, where indicated, the following special stains were employed: Weigert's elastica stain; van Gieson's stain for collagen; periodic acid Schiff; phosphotungstic acid haematoxylin for fibrin and smooth muscle; and the reticulin stain of Gordon and Sweet.

In all patients there was microscopic evidence of widespread atheromatous embolization including the brain, liver, prostate, thyroid, pancreas, spleen, adrenals, stomach, small intestine, kidney and mediastinal lymph nodes. This was most pronounced in the kidneys and spleen; the vessels of the pancreas, liver and gut, while not affected to the same extent, also contained many lesions, and in the remaining organs only isolated vessels were affected. Emboli occurred in vessels varying from 54 to 715 μ in size, but those most frequently affected measured from 150 to 200 μ in size.

In all the larger vessels affected embolization apparently occurred at sites of branching. This was suggested by the frequency with which affected smaller vascular channels were seen in close relation to the main artery, and section at various levels demonstrated continuity of some of these with the main artery. In the kidney cholesterol clefts and the accompanying reaction could sometimes be seen affecting a major artery in the cortex and medulla and all its radicles down to interlobular artery-size.

Whatever the age of the lesion, the atheromatous material appeared as cleft-like spaces conforming in size and appearance to cholesterol crystals (Fig. 3). These may lie longitudinally or transversely in the lumen of the vessel and usually have a constant polarity towards one another, appearing as parallel groups of clefts. Their numbers vary considerably from single clefts occupying little of the lumen, to closely packed clusters which completely occlude the lumen (Figs. 6, 7, 8 and 10).

The clefts in the earliest lesions are outlined by free-lying red cells and usually scanty eosinophilic material giving a negative staining reaction for fibrin (Fig. 4). Sometimes this material contains a few leucocytes. Proliferation of intimal lining cells at the site of lodgement is the first change of the vessel wall (Fig. 7). At about the same time, flattened and elongated cells, which appear to arise from the proliferating intima, are closely applied to the clefts (Fig. 8). Where protein material separates the clefts, these spindle cells extend into it to produce cellular septa and separate and envelop the crystals. These cells become more and more elongated and thinned, and not only resemble fibroblasts but also produce collagen. They may also give rise to foreign-body giant cells which are closely applied to the clefts. Vascularization of the septa occurs in some instances, resulting in the formation of eccentrically placed lumina as seen in the recanalization of thrombus. These channels may even acquire smooth muscle within their walls and resemble arterioles.

At no time is there necrosis of the vessel wall, a significant inflammatory response within or around the vessel, or typical thrombus formation. However, in some of the smallest vessels, the crystal may be as large as the internal diameter of the lumen, thus distorting the vessel into an oval structure. The impacted cholesterol crystal may compress the wall and almost protrude beyond it.

Ultimately, the intima of the affected vessel is much thickened by concentric fibrosis. The lumen is occluded by elongated fibroblastic cells separated by varying amounts of collagen in which the outlines of cholesterol crystals persist, irrespective of the degree of chronicity of the lesion (Figs. 9 and 10). The internal elastic lamina shows pronounced splitting and reduplication with newly formed fibrils extending into the fibrous intima; interruption and fragmentation of the elastica occurs as well. The media appears atrophic and may show focal fibrous replacement. In the larger vessels inefficient recanalization of the lumen is usually evident. The intimal proliferation and fibrosis can usually be seen extending along the vessel beyond the site of the atheromatous embolization.

CHANGES IN ORGANS FOLLOWING VASCULAR OCCLUSION

Infarction or ischaemic atrophy is invariably present if the organ shows many emboli.

The splenic vessels are extensively involved in all patients, the spleen showing extensive, almost confluent infarction. That there have been recurring episodes of embolization is illustrated by the varying ages of the infarcts, some being well on their way to organization. There is also atrophy of the splenic stroma with approximation of the fibrous trabeculae.

In Case 1 the cerebral haemorrhage must also be ascribed to infarction following embolization. The histological appearances at the site of haemorrhage, the unusual site of haemorrhage, and the presence of cholesterol clefts in the related arteries of the brain (Fig. 5), all point strongly to this mechanism. The gut, too, shows lesions of a more acute nature. The sites of maximal embolization are associated with intense mucosal congestion and engorgement of the submucosal venous channels, as occurs in subinfarction.

Surprisingly enough no recent infarcts are noted in the kidneys, although these show the most extensive embolization in all cases. Some sections show large, wedge-shaped cortical areas of glomerular hyalinization and tubular atrophy alternating with normal kidney substance; in others these foci have fused to involve most of the cortex. The changes though are not those of infarction, but of slowly developed ischaemic atrophy. Some of these foci may well be the result of vascular atrophy in a hypertensive patient, but the association between the embolic lesions and the areas of atrophy are so constant that a causal relationship is suggested.

Healed infarction is noted in the prostate and in the pancreas of Cases 1 and 2 – those showing the most striking vascular changes. There is evidence of focal acinar atrophy and of septal fibrosis, but not of a recent or preceding acute lesion. In Case 4, though the vascular lesions are not so obtrusive, there are focal areas of acute pancreatitis. Though these may have been initiated by the embolization, this is by no means certain.

Where isolated vascular lesions exist such as in the liver, thyroid and lymph node, no ischaemic effects are noted.

DISCUSSION

It is generally accepted[1,3,9] that the characteristic, biconvex, intraluminal cleft is the outline of a cholesterol crystal, and our inability to confirm this directly by frozen section is of little moment. There can be no doubt that these crystals are of embolic origin. Sufficient numbers of cases have been described to accept both these statements, and in any event atheroma does not occur in small arteries and arterioles of the size affected in these cases. On the other hand, in all 4 cases, there is an adequate source for the cholesterol on an embolic basis from the widespread and extensively ulcerated aortic atheroma.

Small-sized arteries, from 150 to 200 μ, are most commonly affected and their appearances suggest that impaction occurs most frequently at the site of branching. The very widespread distribution of the lesions indicates that few arteries of the organs are spared, although the vasculature of the kidney, spleen and pancreas, in this order of frequency, are reported to be the most frequently and most extensively involved.[5]

Apart from the characteristic appearances of the clefts and the equally characteristic proliferative intimal response they evoke, there are other features which distinguish these lesions from other occlusive thrombo-embolic manifestations. Firstly, the lack of thrombotic response is a surprising finding. Although the mass of cholesterol crystals may completely occupy the lumen and one might reasonably expect thrombosis secondary to stasis, the usual components of intravascular thrombosis are lacking. Mostly the crystals are surrounded by free-lying red cells, but in some instances they are separated by pink amorphous material resembling protein, which does not stain as fibrin or resemble thrombus. Flory,[1] in describing the early lesions, mentions the presence of thrombus containing cholesterol clefts, but one is left with the impression that this represented a true thrombotic embolus from a patch of ulcerated atheroma. The acute inflammatory infiltrate of the perivascular tissues and of the vessel wall, so common a feature of the organization of even a bland thrombus, is lacking. Similarly, necrosis of the vessel wall is absent, although it would appear likely that spasm may follow the impaction of the embolus, as is suggested by the partial extrusion of the cholesterol crystals in some of the smaller vessels. Histologically, further proof is provided of the 'indestructible' nature of cholesterol in the late lesions. Intimal proliferation with fibrosis results in fibrous encasement of the emboli, rather than replacement, and no matter how chronic the lesions are, the cholesterol clefts persist and retain their form. Certain segments of kidney show occlusion of a main artery and its many branches, as would occur in a progressive process, yet this has happened in the absence of ordinary thrombotic mechanisms. Does this indicate that at the time of embolization this artery and its branches were patent functionally and thus received the bulk of the material discharged into the renal artery?

The relative infrequency of this lesion has been stressed by most authors. Flory,[1] in a survey of 267 cases with severe atheroma, could find evidence of such lesions in only 3-4% and these impressions have been confirmed by the findings of Thurlbeck and Castleman.[3] However, the findings in 2 of our patients (Cases 1 and 2) illustrate that the sequelae may be serious. In the first patient death was due to cerebral haemorrhage almost certainly secondary to atheromatous embolization; the second died with renal insufficiency, and while we cannot affirm that this was due entirely to atheromatous embolism, we are confident that it contributed to the severe damage and failure. Similar events have been recorded in the literature,[8,2] and in addition there are instances of skin ulceration,[13,9] acute pancreatitis[4] and myocardial infarction[6] in which a similar pathogenesis has been postulated.

The systemic effects of this lesion have probably not been underestimated, since ordinary postmortem examination is likely to reveal these very characteristic changes in vessels, if they exist. However, the extent to which similar emboli contribute towards the ischaemia in arteriosclerotic gangrene of the limbs is still an unknown factor. This should be further investigated by widespread selection of sections from smaller vessels as well as the large ones in degenerative vascular disease with gangrene.

SUMMARY

1. Four cases showing extensive evidence of atheromatous embolization are described.

2. In one patient death was directly attributable to the embolization, resulting in cerebral infarction and haemorrhage, and in a second, dying from uraemia, it was at least a contributing factor.

3. The organs most commonly affected by atheromatous embolization are the kidney, spleen and pancreas in order of frequency. The vessels most frequently affected range from 150 to 200 μ in size.

4. Cardinal features of the lesions in the vessels are the presence of highly characteristic biconvex clefts, representing cholesterol crystals, which are enveloped by proliferating intimal cells. The general absence of a thrombotic response at the site of embolization and the persistence of the cholesterol crystals in long-standing lesions, are additional noteworthy features.

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