ARTERIOPATHY IN WALDENSTRÖM'S DISEASE

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Necropsy reports in Waldenström's (1944) disease have been few and unenlightening. This is to be expected in so chemical a disorder as the manufacture of abnormally large globulin molecules, an abnormality that seems suited to the congenital causation recently described (Bottura, Ferrari, and Veiga, 1961). The present report gives, therefore, only a brief report of the disease, its purpose being to throw some light on arterial physiology, in which subject the case has constituted a kind of natural experiment.

Case Report

The patient was a mulatto ship's stoker, 51 years old, 152 lb. (69 kg.) in weight, who complained first of swelling of the ankles and a petechial rash on the legs. He was then found to have a slight lymphocytosis. A year later, his right testis was removed surgically in Australia: two months after this he began to have successive crops of very painful shallow but slow healing skin ulcers on the arms and legs which necessitated hospital care (with septic episodes and amputation of his left leg) until his death five years later. A cryoglobulin found in his blood amounted to between 3 and 4 g./100 ml. of plasma, gave a gelatinous precipitate at 4° redissolved at 37°, migrated in the γ position, and produced an enormous plasma viscosity of about 15 centipoises at 20°, compared with readings up to 1.9 in the normal and 2.5 in the rheumatoid. Estimation of the sedimentation rate at room temperature proved impossible because of gel formation, the appearance in the tube being exactly that illustrated by Stefanini and Dameshek (1955). The diagnosis was confirmed by a great deal of repeated laboratory work: biopsies of skin ulcers showed non-specific inflammation with perivascular lymphocytic infiltration, intravascular clots, endarteritic obstruction, and fibrotic vascular remnants; biopsy of a cervical lymph node (requiring ligation of lymphatics because of milky exudation) showed lymphoid hyperplasia; sternal puncture showed 50 per cent small adult lymphocytes; and blood lymphocytes never rose above 10,000 per c.mm. and were reduced by treatment with nitrogen mustard.

The main necropsy findings were summarized as: (1) arterial degeneration with multiple dissections, subarachnoid hæmorrhage, and colic infarction; (2) serofibrinous pleurisy and fibrocaseous tuberculosis of upper lobes of lungs; and (3) Waldenström's essential macroglobulinæmia with multiple ulceration of the skin of the extremities. The subarachnoid hæmorrhage ensheathed the last inch of the left vertebral artery and the circle of Willis. No abnormality was seen in the small heart (12½ oz., 347 g.), but the arteries showed striking changes. The thoracic and abdominal aortæ were greatly widened, thinned, and folded, so that opening them was like cutting into a partly inflated crumpled paper bag. Extensive "pleats" projected into the lumen in several places: the largest, 5 cm. long, running parallel to the vessel's axis up the left side between left renal and common iliac arteries, indented the lumen to a depth of 1.5 cm., and was glued to the posterior wall by clot of recent appearance. The aortic media enclosed a thin layer of black clot from the ligamentum arteriosum to the seventh segmental branches. Atheromatous pitting appeared continuous throughout thoracic and abdominal aortæ, though no dissections were seen in the latter. A large dissection was present throughout the right common and external iliac arteries in the form of a thin uniform sandwich of red-black clot reaching (11 cm.) to Poupart's ligament. The right popliteal artery was swollen into a fusiform shape for a length of 6 cm., and its wall (up to 0.5 cm. thick) was distended by pink gelatinous material streaked in places by hæmorrhage. Hæmatoxylin and eosin stain of this vessel (Fig. 1 and 2) showed the main part of its wall to consist of floccular eosinophil material, with jigsaw cracks, compatible with completely necrosed media. Except for a few endarteritic vessels, the adventitia was free from abnormality, and, immediately within it,

a thin rind of the only living plain muscle to be found in the vessel had persisted in places. Here, the outermost zone of necrosis contained round, oval, or cholesterol-shaped empty cystic spaces, eosinophil staining was light and hyaline; and there were rare foci of calcification, giving a picture of ectopic atheroma similar to that recently shown (Fig. 4 of Finlayson, Symons, and T-W-Fiennes, 1962) in the thoracic aorta

FIG. 1.—Transverse section of whole popliteal artery (H. and E. $\times 3$).

FIG. 2.—Transverse section of whole thickness of wall of popliteal artery (H. and E. $\times 13$). The bulk of the wall is necrosed media. One corner shows thrombus in the lumen, while at the opposite (outer) edge a pale hyaline zone separates necrosed media from the rind of surviving media immediately beneath the ragged adventitial covering.

of a grey parrot. The intimal coat was hardly distinguishable from the lining of clot. The popliteal vein was normal. In the thoracic aorta, the same changes were rather less advanced, and the dissecting hæmorrhage (up to 2.5 mm. thick) occupied the most normal (outer) part of the media. The right common iliac artery showed intimal atheroma, a large patch of medial calcification, and a sheath of hæmorrhage in the necrotic media, whose structure, as above, was that of a marbled network of eosinophil curd. Small vessels throughout the tissues were only seldom the site of endarteritis, and very seldom of perivascular inflammation. The above findings were taken in sum to indicate Erdheim's (1930) idiopathic cystic medionecrosis. No medionecrosis (nor micro-angiitis, nor skin ulcers) was recorded in McFarlane *et al's* (1952) complete necropsy report of Waldenström's disease, though "the vascular system was clogged with viscous protein".

DISCUSSION

Ischæmia due to cold-induced viscosity of the blood seems a reasonable way to explain the skin ulcers and their distribution, without invoking a general micro-angiitis. Disease in the arterial wall is not then required by the pattern of the case to follow disease in the vasa vasorum, where, in fact, only negligible lesions were seen. Therefore it is suggested that the seepage of macromolecules from the blood stream has given rise in the course of six years to medionecrosis.

Orthodox histology states that the vasa vasorum of large arteries "do not penetrate further than the external layers of the media" (Maximow and Bloom, 1942). Hewer (1944) describes how "lymph circulates freely in the intima and media coats, diffusing from the plasma in the lumen of the vessels and passing easily between the fenestrated elastic laminae." Contradicting this, Ham (1953) points out the greater likelihood of colloid accumulations in arterial walls than elsewhere, because "patent lymphatic capillaries could not be expected to be present in those layers of the walls of arteries that bear the brunt of arterial pressure." Hueper (1942) showed that infusion of macromolecules in rabbits, rats, and dogs led to atheroma-like lesions.

The arrangement of an arterial wall, with its fenestrated elastic membranes containing pores about 2μ diameter, is very suggestive of the Buchner filter. The efficiency of such filters depends on their pressure differential and on the viscosity of the fluid filtered. They become permanently blocked in any portion to which a sludge of particles larger than their pores can gain access. A rise in pressure will temporarily improve filtration rate of viscous fluids at the expense of general clogging later. Since a capillary will pass lymph, arterial endothelium under pressure should pass more viscous fluids. If a flow of nutritive fluid occurs from intima to adventitia due to pressure filtration rather than diffusion, there is reason for macromolecules to cause ischaemia through viscosity, without the sludge effect invoked to explain local patches of atheromatous degeneration. Viscosity, by acting on the whole cylindrical filter-bed, would cause ischaemia of a length of artery, while, on the contrary, an atheromatous plaque could be by-passed by the flow beneath it "in the direction of the long axis of the vessel" (Hewer, 1944).

This idea seems capable of extension to arteriopathy in general and has a certain convenience in connecting pressure (hyperpietic) and blockage (lipæmic or macromolecular) theories of ætiology. Both factors could affect nutrition by altering mural filtration rate, either widely, as in the present case, or locally where the current impinges, as at an ostium in atheroma. A gush of adrenaline might push more fluid into arterial walls, and a prolonged state of shock (e.g. in burns, diphtheria, or enteric fever) might slow the rate below nutritional level: both these conditions are recorded causes of atherosclerosis (Anderson, 1953).

SUMMARY

A comparison between the elastic laminae of arterial walls and a Buchner filter is put forward as an explanation of medionecrosis occurring in a fatal case of Waldenström's macroglobulinæmia of six years' duration.

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