Plasmatic vasculosis resulting from dysoria *

A modern confirmation of Aschoff's holistic view on vascular diseases.

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When in Dundee, Donald McKay, Professor of Pathology at Columbia University, produced the pregnant aphorism, "Medicine without histopathology is like history without geography". Some twenty miles from Dundee geographical technique illuminated history, notably in Dr. St. Joseph's aerial photography with its revelation that a Roman camp, already excavated at one corner, extends over an area vastly greater than the archaeologists had ever imagined.

In studies on vascular disease, Aschoff, being a genius, made fertile guesses that went well beyond facts revealed by the techniques then available. Now, with newer techniques, evolved by the group with whom I work, not only can Aschoff's guesses be confirmed, but we can see that the field stretches further than clinicians or pathologists had ever imagined.

In his writings, Aschoff (1924) mentions "the invading stream of plasma" and this he suspected must **normally** be traversing **arterial** walls outwards from the lumen, basing his concept in part at least on the observation that in atheroma a fatty material accumulated against the inner face of the internal elastic lamina. This seemed to him to be validated by the fatty accumulation at the same site in the hyperlipaemic experimental animals of Anitschkow. But fat is not an ideal marker; fat **might** be formed locally by breakdown of ischaemic tissues. It is sad that Aschoff had no staining method for fibrin able to provide at the same time a satisfactory delineation of the tissues of the site. This probably explains the strange fact that he scarcely mentioned fibrin in his discussion.

Our technical interest in the demonstration of fibrin led us unexpectedly from acute rheumatic disease to the florid lesions of arteries and thence via the kidney of diabetes mellitus to the slowly developed and less gross lesions of so-called chronic arterial disease. As in so many biological matters, the process of our technical and our observational studies was one of many interacting and altering themes. "The historical process is a unitary transformation, a complex form steadily transforming itself, and is too rich for the thread of language to portray in a single sequence" (Whyte 1950). The thread of his brief narrative is the confirmation of Aschoff's guesses, and the incidental possibilities of proceeding from that position to further unifying concepts in the understanding of vascular disease.

The study of fibrin as a deposit within a vessel wall has the advantage that fibrin is a substance of known ancestry. It is certainly the progeny of fibrinogen, although it may appear in different forms, the site of its genesis possibly determining its structural constitution as it certainly does its fate. Further, since its sire, fibrinogen, is normally confined to the circulating plasma, we can reasonably regard deposited fibrin as proof that plasma had carried fibrinogen to the spot. Fibrin coagulated within the walls of blood vessels, fibrinous vasculosis (Lendrum 1955), is manifest as a deposition between the tissue structures of the wall.

Brief mention may be made here of two other extraluminal reactions for fibrin, which are not inter-structural. The first may not, in fact, be due to fibrin although the material reacts with all our methods for fibrin; this is the conglutination of the striation bands occurring in the early stages of degeneration of cardiac muscle (Barclay 1961). The second reaction is dependent on the occasional uniform hyalinisation of frankly necrotic cells, a phenomenon commonly attributed to seepage of plasma into the necrotic mass. Leaving aside these non-specific reactions, we may say that fibrinous vasculosis is brought about by the intrusion of plasma through the endothelial lining.

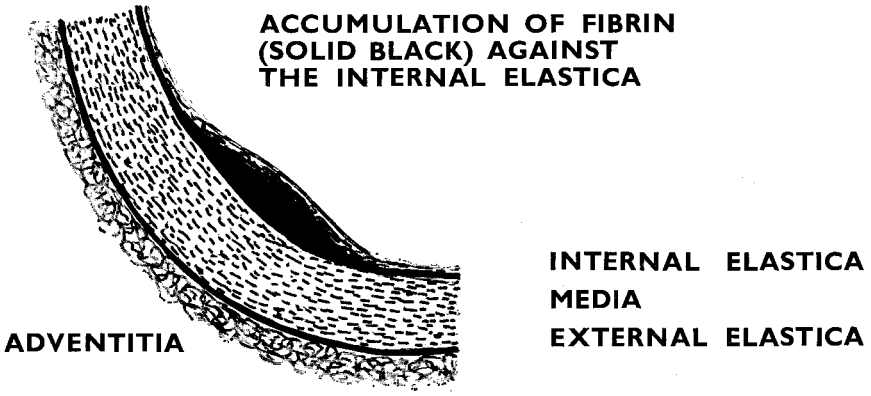
The term dysorie, now anglicized to dysoria (Schloss 1948), was coined by Schurmann and MacMahon (1933) to express an upset in permeability manifest by a greater than normal escape of luminal contents. It has to be remembered that the old term exudation was applied at the level of capillaries, and further that visible structural change in the capillary wall was at that time beyond most microscopists. Then in 1933, Schurmann and MacMahon demonstrated emphatically that deposition of fibrin occurs in the walls of arterioles and arteries as a result of plasmatic intrusion. The concept of an upset merely in permeability seemed too narrow to Meyer (1950) who regarded the essential mechanism as a "Blutplasmaphorese" but even if he failed to give adequate credit to the earlier workers he has given us a useful word in "insudation" to imply the exuding of plasma from the lumen and its trapping within the wall of the vessel. It seems perfectly proper to regard Schurmann

* Paper read at the Medical Congress, Kitwe, May 1068.

and MacMahon's dysoria as an excessive traverse of plasma, into the wall (insudation) and even beyond. This arises either from upset of vascular permeability or of the inter-luminal pressure or of both, occurring intermittently or persistently, rapidly or slowly, mildly or intensely. When the results of dysoria are revealed by the deposition of fibrin we may reasonably call this fibrinous vasculosis, and with modern techniques this is recognizable in arteries, arterioles, capillaries and venous sinuses.

Fibrinous vasculosis in arteries in its florid form is particularly well seen when an extreme pulmonary hypertension complicates mitral stenosis. In such necropsy material we have found many arteries with an accumulation of fibrin compacted against the internal elastic lamina, as in figure 1. An exactly similar disposition occurs in systemic malignant hypertension, notably in renal arteries of the size of the arcuates, and in induced local hypertension as occurs in the mesenteric and renal arteries after resection of an aortic coarctation.

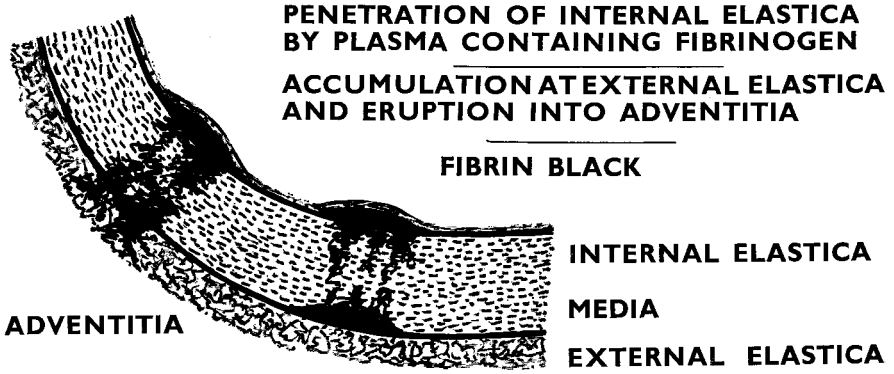
Fig. 1



Further extension of the invading stream, as revealed by the situation of the fibrin, is shown in Figure 2. The fibrin is now seen "straggling" across the media and beginning to accumulate against the external elastic lamina, a barrier that seems less likely to be blocked than the internal lamina; from there the plasma reaches the less restricting tissues of the adventitia, and the outspread fibrinous deposit may even look like an explosive outburst. These florid changes may be unaccompanied by any aggregation of round cells or polymorphs, but where this occurs we believe that it is secondary to rapidly effected necrosis of the medial muscle and this we attribute to a particularly dense aggregation of fibrin against the internal elastica with a consequent ischaemia of the related media. This incubus of fibrin with suffocation of the underlying media is seen in identical form in the arteries of polyarteritis nodosa. If survival permits the evolution of the so-called healed stage, we find arteries showing zones of vanished internal elastic and media alongside zones of persistent elastic exactly overlying portions of surviving medial muscle. This picture I have now found both in pulmonary malignant hypertension and in polyarteritis nodosa.

The remarkable similarity, revealed by the new methods, of the fibrinous vasculosis in severe hypertension and in polyarteritis nodosa surely indicates an intense degree of dysoria in the two conditions, but the cause of the dysoria is almost certainly different. It is not illogical, in view of what is already known, to attribute the fibrinous vasculosis in hypertension to an excess of luminal pressure, forcing into the wall not only plasma but also colloids normally retained in the lumen ..... one need only recall its occurrence in malignat hypertension, both systemic and pulmonary, in the mesenteric and renal arteries after resection of a coarctation, and in the venous sinuses as well as the arterioles and arteries

Fig. 2



in infarcted tissues and areas affected by torsion. The occurrence of dysoria in polyarteritis nodosa is perhaps the mark of the hyperergic lesion in the vascular system, and it is tempting to suggest that all hyperergic vascular diseases are characterised by a focal dysoria, dependent on focal zones of hyperpermeability and possibly without any hypertensive element. In urticaria the focal escape of fluid carries little colloid, but ranging from this we have the various permeabilities of greater degree, allowing larger molecules to escape, fibrinogen and up to the erythrocytes of purpura. The size of vessel involved varies greatly, and possibly significantly, whether we deal with the "flea-bitten kidney", systemic lupus erythematosus, some of the primary nephrotic kidneys, thrombotic thrombocytopenic purpura or the drug induced purpuras. In following Whitehead's advice to seek simplicity but mistrust it, we would be wise to avoid too Procrustean an attitude. None the less the florid fibrinous vasculoses and the concept of dysoria all go to support the validity of Aschoff's "invading stream of plasma".

If we now consider again the lung, we see the alveoli around those arteries showing fibrinous vasculosis are filled with fibrinous network. This acellular deposit of fibrin occurs only in the peri-arterial alveoli, providing a further evidence of Aschoff's traversing stream of plasma.

Study of the less intense vasculoses with their greater duration has been particularly illuminating in the kidneys from cases of diabetes mellitus with onset in maturity. The findings have been reported elsewhere (Lendrum **et al** 1962, 1964, Lendrum 1963), and all that need be said here is that the new methods have elucidated the morbid processes, and revealed with clarity that the changes of ageing happen to fibrin. Fibrin deposited in the extraluminal tissues, unassailed by fibrinolysins from the circulating plasma or from inflammation, undergoes some intrinsic alteration in its structure so that, athough the shape of the deposit remains meanwhile unaltered, the fibrin loses its ability to bind the small molecule dyes that stain fresh fibrin, and eventually takes the large molecule dyes that stain collagen. This hyaline acellular material, meriting the name pseudo-collagen (Lendrum 1961), has had its ancestry unequivocally established in these diabetic kidneys (Lendrum 1963), and has encouraged us to pursue the idea that this aged fibrin is perhaps the material in the late thickened atheromatous intima described by Aschoff as a "sort of hyaline substance".

The concept that pseudo-collagen implies a previous fibrinous vasculosis seemed a rather risky basis for retrospective interpretation of chronic vascular diseases. It has been made even more shaky by our recent finding that amyloid in the deposits in the tissues undergo ageing changes and may eventually become a hyaline material that takes the large molecule acid dyes characteristically taken by collagen, in other words amyloid, like fibrin, ages and becomes pseudo-collagen. None the less, as reported elsewhere (Lendrum 1964), it is quite clear that in the chronic changes of arterial disease one finds an acellular hyaline material, that merits recognition as pseudo-collagen, in the same sites as are occupied by fibrin in the florid forms of fibrinous vasculosis. A notable similarity to the florid lesion is shown by the association in chronic lesions of a specially dense accumulation of pseudo-collagen in the deepest part of the intima with a distinct atrophy of the underlying medial muscle. Further, if the renal arteries from cases of benign hypertension show no obvious thinning of the media, special staining may well reveal that the muscle cells, small, compressed and often with pyknotic nuclei, are separated from each other by an intrusive gel, a hyaline structureless material containing neither nuclei or any other particulate thing, like a lava that had flowed into the village and was crushing the separated cottages, and it stains with the collagen dyes.

The deposit of pseudo-collagen in the intima can, I believe, be reasonably interpreted as the product of fibrin and as Aschoff's "sort of hyaline stuff", thus confirming his guess that it came from the lumen, carried thence in his "invading stream of plasma". The further extension of this stream into the media raises the interesting possibility that the so-called fibrosis of the media is in fact a pseudo-collagenosis.

The particular susceptibility of the diabetic vessels to pseudo-collagenosis would seem to be primarily due to increased permeability. The hypertensive element commonly present in the older diabetic cases is probably secondary to vascular narrowing, although it would then surely aggravate the process. If we could understand or inhibit the vascular changes in diabetes we might well be on the way dealing with atheroma and arteriosclerosis. We already have many and some valuable hypotensive agents. Perhaps we owe it to Aschoff to look more actively into the possibilities of therapeutic agents that would attack the other aspect of dysoria, drugs that would depress permeability.

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