SOME PATHOLOGICAL ASPECTS OF ARTERIAL DISEASE

By T. Crawford, B.Sc., M.D.

Department of Pathology, St. George's Hospital Medical School, S.W.1

The term arteriosclerosis was first used as long ago as 1833 by Lobstein. He used the word in a generic sense to indicate the group of morbid conditions of the arteries characterized by thickening and hardening of the vessel walls, and it is best to retain this generic connotation of the word. Hardening of the wall may arise from changes occurring either in the media or in the intima. The medial lesion may take the form either of fibrous replacement of muscle often followed by hyaline degeneration of the collagen fibres, or of calcification or there may be a combination of these two lesions. The intimal lesion also has two main components: overgrowth of the fibrous tissue and the development of foci of lipoid material in the intima, often accompanied by calcification.

In this paper it is proposed first to describe the main conditions in which these changes occur before proceeding to a discussion of the aetiology and pathogenesis of the most important member of the group—atherosclerosis.

Ageing Changes in Arteries

The structure of the arteries undergoes a gradual change from birth to old age. The change consists of gradual fibrous replacement of medial muscle and increase in thickness of the intima. It is well seen in the coronary arteries which at birth have an extremely thin intima and a high proportion of muscle in the media (Fig. 1). Even by the age of 10 years the intima is already much thicker (Fig. 2), and by 40 years the proportion of collagen fibres to muscle in the media has risen greatly (Fig. 3). These changes are accompanied by some elongation and dilatation so that at advanced ages it may be regarded as normal to find rather rigid, dilated and slightly tortuous arteries. These changes do not in themselves cause any ill-effects, but the borderline between normal and abnormal is an indistinct one and similar changes occurring in earlier life must be looked upon as pathological. The term precocious senile arteriosclerosis may be applied to this state. Here again the effects are likely to be slight unless there is coexistent atherosclerosis (v.i.).

Fig. 1.—Coronary artery of newborn infant showing extreme thinness of intima. Elastic stain, × 200.

Fig. 2.—Coronary artery of a boy aged 10 years showing increasing thickness of intima. Elastic stain, × 75.

Fig. 3.—Medial coat of coronary artery from a man aged 40 years. The muscle fibres (deeply stained) are widely separated by collagen fibres. Mallory's stain, × 400.
Hypertensive Arteriosclerosis

The structural changes occurring in the arteries as a result of hypertension may resemble closely the changes occurring at advanced ages which have just been outlined. When, however, hypertension develops in a young subject the stage of fibrosis is preceded by a hyperplastic phase during which the amount of muscle and elastic tissue in the vessel wall may be much increased; but as the condition progresses the hyperplastic muscle is gradually replaced by fibrous tissue, though the excess of elastic fibres often persists, especially in the arterioles (Fig. 4). When hypertension develops in older subjects this hyperplastic phase is trivial or altogether suppressed. Concentric thickening of the intima in the smaller vessels is often a very conspicuous feature.

Once more it must be said that these changes have little effect unless, as all too frequently occurs, atherosclerosis becomes superadded.

Mönckeberg's Sclerosis (Calcification of the Media)

In 1903 Mönckeberg described a variety of arteriosclerosis in which deposition of calcium salts in the degenerating elements of the media was the most conspicuous feature, and this condition has come to be known by his name. It is seen principally in elderly subjects and the medium sized arteries of the limbs and head are those chiefly involved. The calcification is often patchy and may form rings, giving the vessel an appearance reminiscent of the trachea; at other times uniform calcification occurs over a stretch of the vessel giving it a pipe-stem character. Microscopy (Fig. 5) shows the calcium salts as a granular deposit in hyaline collagen and fatty muscle fibres in the media. There is sometimes formation of actual bony trabeculae in longstanding cases.

Mönckeberg's sclerosis is often regarded as a distinct pathological entity, but there is little justification for this view; there is progressive increase in the calcium content of the media with advancing age (Lansing, Blumenthal and Gray, 1948), and this feature becomes exaggerated in arteriosclerosis from whatever cause. The cases described as Mönckeberg's sclerosis are merely those in which the medial calcification attains a sufficient degree to be recognizable by the naked eye or the palpating finger, or to be visualized by X-ray examination.

Atherosclerosis

Atherosclerosis with its concomitant thrombosis is responsible for an enormous morbidity and mortality, far outstripping, for instance, the mortality from tuberculosis and all forms of malignant
disease. It is therefore appropriate to deal at much greater length with the pathology and pathogenesis of this variety of arteriosclerosis.

The term atherosclerosis is used to imply the presence of accumulations of lipoid material in the intima together with widespread intimal thickening from fibrous tissue proliferation. In the early stages the lipoid accumulations form discreet yellowish plaques lying closely beneath the vascular endothelium and at this stage the term atheroma is appropriately applied. As the condition advances the plaques enlarge and may coalesce, and ulceration, fibrous tissue proliferation and calcification occur in an irregular manner (Fig. 6). The ulcerated areas tend to blacken from absorption of pigment and they often become covered by thrombus. Considerable tracts of intima may become much distorted in this way, but the lesion remains essentially of a patchy and asymmetrical nature. Any part of the arterial tree may be involved, but the abdominal aorta, iliac arteries, arteries of the lower limb, renal, coronary, carotid and cerebral arteries are particularly susceptible. The atheromatous plaques have a tendency to cluster around the points of bifurcation and the sites of origin of branches of arteries. The distribution of lesions in a given case is quite unpredictable; it is not uncommon to find a single vessel severely and even fatally involved while the remainder of the arterial tree is almost free of the disease.

In an excised segment of artery the plaques appear to protrude into the lumen of the vessel producing a characteristic signet ring deformity, but this is much less evident when the vessel is distended by the normal blood pressure (Crawford and Levene, 1953). The plaque then appears embedded in the wall of the artery, lying in a cavity formed by thinning of the media (Fig. 7). Duguid (1954) has stressed that unless there has been recent thrombus deposition over the plaque the lumen will not be significantly narrowed and may in fact be dilated.

Microscopic examination shows that in the early stages the lesion consists merely of an aggregation of mesenchymal cells distended with lipoid material rich in cholesterol lying in the superficial layers of the intima. This early lesion may well be reversible, though the point has not been determined with certainty. In more advanced lesions some of the lipoid material lies free in the tissues and a layer of hyaline collagen of varying thickness separates the fatty debris from the lumen. There is always some degree of medial thinning in relation to the fatty plaques in the intima. As the intima in the most severely affected parts becomes progressively thickened a network of abnormal capillaries extends into it, taking origin from the vasa vasorum or from the lumen of the artery itself (Winternitz et al., 1938; Geiringer, 1951; Crawford and Levene, 1955). Interference with the blood flow in these capillaries may result in necrosis and ulceration of the plaques which in turn may initiate thrombus formation in the artery.

The Pathogenesis of Atherosclerosis

The way in which the lesions develop has been the subject of much discussion and experiment, and considerable evidence has accumulated that disturbed cholesterol metabolism and the occurrence of mural thrombosis play important parts.
The Role of Cholesterol. It was as long ago as 1847 that Vogel demonstrated the presence of cholesterol in atheromatous plaques, and it is not surprising that much attention has been focused on the problem of how it gets there. Anitschkow's demonstration in 1913 that atheroma-like lesions developed in the aortas of rabbits when pure cholesterol was added to the diet initiated a continuing flow of experimental work. Lesions resembling human atherosclerosis have been produced not only in the rabbit but also in the dog (Steiner and Kendall, 1946) and the chicken (Dauber and Katz, 1942) by procedures designed to maintain a raised level of the blood cholesterol over prolonged periods. The mechanism by which the lipid material gets into the arterial wall in these experimental animals has been recently elucidated by Rannie and Duguid (1953), who demonstrated that cholesterol-bearing cells circulate in the blood and adhere to the arterial walls. These deposits then become covered with endothelium and in this way are incorporated in the intima. Leary (1941) had earlier observed these foam cells in the blood of cholesterol-fed rabbits and demonstrated their origin from the Kupffer cells of the liver. It seems, therefore, that the course of events in the experimental production of atherosclerosis in cholesterol-fed animals is well established, and we must consider whether this knowledge throws any light on the pathogenesis of the disease in the human subject.

The Blood Cholesterol in Man. Experimental atherosclerosis in animals only occurs as the result of procedures which lead to persistent elevation of the blood cholesterol level. It is therefore essential in considering the relationship between the experimental lesion and the disease in man to answer two questions: first, is atherosclerosis especially severe in people with elevation of the blood cholesterol as the result of independent diseases? and second, is the blood cholesterol increased in those with severe atherosclerosis?

The diseases most characteristically associated with hypercholesterolaemia are diabetes mellitus, hypothyroidism, the nephrotic syndrome and essential (familial) xanthomatosis. Of the frequency and severity of atherosclerosis in the diabetic there can be no doubt (Warren, 1938), though its correlation with degree of hypercholesterolaemia is less distinct. Increased severity of atherosclerosis in the other conditions associated with raised blood cholesterol is less definite, but the balance of evidence supports its occurrence in hypothyroidism and in familial xanthomatosis (Hueper, 1944, 1945).

The converse question as to the occurrence of hypercholesterolaemia in patients with manifestations of active atherosclerosis has received as many negative as positive answers. Peters and Van Slyke, summarizing the position in 1946, concluded that no general disturbance of lipid metabolism had been demonstrated in atherosclerotic patients, but it is only fair to add that some subsequent work supports the opposite view (Boas, Paretts and Adlersberg, 1948; Gertler, Garn and White, 1950). Fresh light has been shed on this apparent paradox by the work of Gofman and his colleagues in California (1950, 1951). These workers have studied the behaviour of the serum lipoids and lipo-proteins in the ultracentrifuge. They classified the lipo-protein complexes according to the rate at which they migrate against the centrifugal force in Sf units and showed that Sf 12-20 lipo-proteins increase in concentration with advancing age and are significantly raised in the victims of atherosclerosis as compared with normal control subjects of the same age. This promising though complex work clearly requires confirmation and further study.

The Lipid Content of the Diet. The level of the plasma cholesterol in man is but little influenced by the cholesterol content of the diet, but Keys (1950) has shown elevation of the plasma cholesterol to occur on a high fat diet. The significance of this in the causation of atherosclerosis is scarcely capable of experimental assessment, but observations on the geographical and racial incidence of atherosclerosis and on its incidence during periods of enforced fat deprivation may have some bearing on the matter. The death rate from coronary thrombosis—an acceptable index of the prevalence of atherosclerosis—is found to be highest in those countries with the highest fat consumption in the diet and lowest in those subsisting on a low-fat, high-carbohydrate diet. There are, however, many other variables to be considered such as total calorie intake, expectation of life and racial influences. Nevertheless, when allowance is made for these factors, the evidence supports the association between a high fat diet and a high incidence of atherosclerosis (Rosenthal, 1934). Further support for this association comes from consideration of the statistics for countries suffering dietetic restrictions in war-time. Thus Dedichen and Ström (1948) found a marked reduction in the death rate from cardiovascular disease in Norway between 1939 and 1945 and noted that this fall corresponded closely to the reduced fat content of the diet.

A different approach to this problem has been taken by Fullerton, Davie and Anastasopoulos (1953), who have shown that the ingestion of a meal rich in fat is followed by a period of increased coagulability of the blood, an observation which may indicate the relationship between
the parts played by cholesterol and by mural thrombosis.

The Role of Mural Thrombosis. Duguid in 1946 studied the histology of atherosclerosis in the coronary arteries and came to the conclusion that many of the lesions classified as atheroma resulted from the organization of thrombi. In 1948 he extended his observations to the aorta and found mural thrombi to be frequent. He pointed out that recurrent thrombosis led to progressive thickening of the intima and that subsequent fatty changes led to the typical appearances of atherosclerosis. Duguid’s observations have now been repeatedly confirmed and some further details have been worked out regarding the process of incorporation of the deposits in the intima (Harrison, 1948; Geiringer, 1951; and Crawford and Levene, 1952). There is now no reason to doubt that these mural encrustations play an important part in the development of the full pathological picture of atherosclerosis. The factors governing their deposition and localization remain to be elucidated.

Other Factors

There are probably many factors other than those mentioned above which have some bearing on the pathogenesis of atherosclerosis. An endocrine factor is suggested by the sex incidence: females before the menopause are much less frequently affected than males of the same age, but the incidence in older women approaches closely to that in men. The increased incidence and severity of atherosclerosis in hypertensive subjects and the clustering of lesions around areas where the vessels are weakened by branching suggests that mechanical strain on the vessel plays a part at least in determining the localization of the disease; while the increased incidence in professional as compared with manual workers suggests the possibility of some psychosomatic link-up. For the present, however, all these remain matters of conjecture.

Conclusion

The problem of the pathogenesis of athero-

sclerosis is at the stage where a mass of information and evidence has been accumulated, but it is difficult to be sure of what is significant. It seems to be established that the disease is associated with subtle disturbances of lipid metabolism; that these are more liable to occur on a high fat diet than on a low fat diet; and that intraarterial thrombus formation plays an integral part in the development of the disease as well as being its chief complication.

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T. Crawford

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