ARTERIAL SURGERY

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FOREWORD

PER VIAS NATURALES

When the supply of food, of oxygen, or of both to a cell, a group of cells, an organism or a community is significantly reduced below the level of normal requirement, functional efficiency is impaired, nutrition suffers and in extreme circumstances death occurs. The situation can be alleviated or even restored to normal by timely adequate improvement in the supply of nutrients and of oxygen. To the starving individual or community the problem seems simple. The need is for more food, brought as soon as possible by any means available to circumvent the obstructions affecting the normal routes of supply. Arterial insufficiency and ischaemia illustrate these principles on a small, precise scale. Their cause is arterial obstruction, either occlusive or stenotic. The net final effect depends upon the interplay of the obstructive lesions and compensatory mechanisms such as collateral circulation.

Although the arteries are living tubes and subject to vasomotor control, the concept of vasospasm has largely disappeared from current thought regarding arterial insufficiency. Some degree of dilatation of the collaterals may be brought about by sympathectomy, but this procedure has its most important role in abolishing vasoconstrictor impulses to the skin of the digits when the latter are threatened with gangrene. For the most part the surgery of ischaemia has become much more direct and in respect of the largest vessels rather simple. These may be replaced completely or bypassed by tubes of cloth, woven or knitted from synthetic fibres, or they may be opened, the diseased intima and adherent thrombus removed, and closed again by suture. Medium-sized arteries may be treated similarly, though the current tendency is to use autografts of vein for bypass or as patches. Occasionally bypasses of homograft vessel or of prosthetic material are still used. Some of the most challenging technical problems are presented by vessels of this size, severely stenosed or occluded by thrombosis or embolism, particularly the carotids, the renal vessels and the superior mesenteric artery. The ultimate challenge lies probably for the moment in the coronary arterial system.

Arterial degeneration is the pathological basis of ageing. With the rapid accumulation of knowledge regarding the factors that accelerate it, we may expect to learn how to retard this inevitable process. Similarly, increasing understanding of the astonishingly complex processes involved in blood clotting and fibrinolysis offer hope of major non-operative contributions to therapy. At the present time, however, operative surgery dominates the therapeutic scene, supported by a wealth of technical, pharmacological

and physical modalities—instruments, anticoagulant and fibrinolytic drugs and biological products, control of temperature and of ambient pressure and so forth.

The Scottish Conference on Arterial Surgery at Law Hospital, Lanarkshire, on 11–13 January 1963, made medical history, for this excellent and timley enterprise was conceived, organized and brought to fine fruition by the staff of this large, busy but non-teaching hospital and to them great credit is due. The participants included some of the best-known British authorities on the management of arterial disease. Their contributions and the reported discussions, which together constitute a valuable record of the present position in this field, make good and profitable reading.

W. ARTHUR MACKEY

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THE PATHOLOGY OF ATHEROMA

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MUCH experimental work has been done on the pathology of atheroma, but it is extremely difficult to know how much of it is relevant to what we find in the natural disease in man. In this brief survey I will speak first about the findings in the human disease and then consider the possible importance of some of the experimental findings.

DEFINITION OF ATHEROMA (ATHEROSCLEROSIS)

The pathology of arterial disease in man is difficult to study in this country because there are several very common arterial diseases and these often occur together making it extremely difficult to sort things out. For example, in the course of ageing, certain physiological changes occur in the arteries: there is an increase in the fibrous tissue and calcium content of the vessel wall and sometimes dilatation of the lumen; this could be called " physiological senile " arteriosclerosis. Similar changes, more marked and at an earlier age, occur in people with hypertension, and some pathologists refer to this condition as " hypertensive arteriosclerosis ". We often find calcification of the media of muscular arteries and this appears to be different from the forms of arteriosclerosis which I have just mentioned. All of these conditions have similarities to the lesions of atheroma (or as some call it, " atherosclerosis ") but most experienced pathologists agree that atheroma should be distinguished from the other conditions whenever this is possible. While it is easy to classify arterial diseases in a book, it is sometimes a very different matter to distinguish them in practice.

The typical lesion of atheroma is a focal deposition of lipid in the intima of the artery, usually associated with localized intimal fibrosis. However, in the view of some very experienced and competent pathologists like Professor Dible (1956) too much stress has been laid on the presence of cholesterol and allied lipids in the intima of the vessel, and all atheromatous lesions do not contain cholesterol. Dible considers the oedematous avascular connective tissue which is frequently found in the intima of the smaller vessels of the leg in patients with gangrene, to be atheroma, although it does not always contain fat, and he points out that it is not always possible to say with any certainty where the physiological changes of senility end and the pathological changes

of atheroma begin. The consequences of the ill-defined nature of atheroma upon the interpretation of experimental work in animals must be immediately apparent.

QUANTITATIVE ASPECTS

It has been said that science is measurement and there are problems when one tries to measure the amount of atheroma in a vessel or in a body in the pathological laboratory. Various methods have been tried and none of these are completely satisfactory. Anderson *et al.* (1959), in a study of atheroma in the aortas of Europeans and Bantu in South Africa, used visual grading of lesions and obtained a satisfactory correlation between this and aortic weight and intimal lipid and cholesterol values. There were two points of interest, however. (1) The aortic calcium correlated with atheroma in the Europeans but not in the Bantu. (2) The difference in amount of aortic atheroma seen in the two populations seemed inadequate to explain their different rates of myocardial infarction. It is noteworthy that it is sometimes very difficult to measure the area of a vessel affected by plaques especially in old patients where the edges of the plaques are ill defined.

A completely different approach to the quantitative aspect of atheroma, perhaps the most significant, is to measure the number of partial or complete occlusions, particularly in small vessels. This ties up with the clinical method which has been used to measure atheroma, i.e. the recognition of significant ischaemic effects. In general, atheromatous occlusion of small vessels, such as the coronaries, is related to the overall amount of atheroma in an individual, but there are many exceptions. It is worth noting that the amount of degenerate fat and fibrin in an ordinary aortic plaque may be enough to occlude much of the coronary arterial tree completely. Many studies of atheroma, particularly those relating to metabolic factors, have been based on comparisons between people with and without a history of myocardial infarction. This is a reasonable but by no means fully satisfactory indication of atheroma as is illustrated in the following cases. A woman aged forty died several hours after the onset of severe constricting chest pain. She had a thrombus in her left main coronary artery near its origin and superimposed on a single atheromatous plaque which was calcified; this was the only atheromatous plaque which could be found in her body. (Here would have been a beautiful opportunity for arterial surgery if the patient had survived sufficiently long, and if there had been any way of recognizing that she was suffering from such a localized lesion.) If this woman had survived she might have been included in a study as a case of severe atheroma.

The second case illustrates how we may find very severe atheroma of the aorta and the coronary arteries in people who apparently have nothing wrong with them. A survey was made of the personnel of a factory with full clinical history and extensive electrocardiographic examinations; one man of forty,

who appeared well, died within a few weeks of acute myocardial ischaemia. A coronary angiogram was done at post mortem and the patient was found to have several old coronary occlusions which must have been present at the time of the clinical survey. The clinical assessment of atheroma is thus fair, but very crude; there are obviously many factors other than atheroma which influence the production of clinical disease, and of these the development of collateral circulation is probably of extreme importance.

The Formation of Atheromatous Plaques

This subject has been dealt with fully by Morgan (1956). There are at least two important views concerning the formation of atheromatous plaques. Virchow proposed that filtration of fat from the vascular lumen into the intima of the vessel leads to accumulation of fat in the intima; degenerative changes in the intima are perhaps secondary to the appearance of lipid, or perhaps the intimal degeneration develops first and the filtered lipid accumulates in the degenerate material. The appearances presented by the intimal streaking found in the arteries of young people strongly favour the filtration theory. The lesions are usually quite deep in the intima, and it seems unlikely that material which has first formed a surface layer could be responsible for this type of lesion. In experimental animals plaques develop in a similar position apparently without any thrombus formation, and autoradiographic studies have demonstrated that fats are filtered through the intima of the vessel and tend to settle out just inside the internal elastic lamina.

Duguid has revived the theory of Rokitansky that at least some atheromatous plaques are the result of material being layered on the surface of the vessel. In some atheromatous plaques the lipid is found just under the endothelium. Small fibrin thrombi are often readily demonstrated on the surface of apparently healthy vessels, and these small thrombi are now known to be incorporated into the intima of the vessel in a few days. Fatty change has been demonstrated in experimental thrombi in animals (Nestel, 1959). It is interesting that if one looks at advanced atheromatous plaques in man, one finds that they are laminated and have apparently developed as a result of events of an episodic nature rather than from a continuous process. Furthermore, it is often very difficult to distinguish between atheromatous material and thrombus which is beside it. It has been shown by various methods that nearly all atheromatous plaques contain a lot of fibrin.

Effects of Atheroma

These are well known and include occlusion of arteries with or without thrombosis, embolism from the plaques and the formation of aneurysms.

There is a curious finding in most " atheromatous " aortic aneurysms and occlusions—a marked inflammatory reaction in the aortic wall in addition to the degenerate atheromatous material. Halpert *et al.* (1958) suggested that the

inflammatory lesion may be of considerable importance in such cases, and the finding by Pepler and Simson (1959) that a similar inflammatory condition may affect the lower end of the aorta and the iliac vessels in the Bantu in whom severe atheroma is uncommon, raises the question of whether atheroma has much to do with serious complications in the abdominal aorta. Certainly, if we did not have the Wassermann reaction to recognize syphilis, many young pathologists would regard syphilitic aneurysms as atheromatous, as these are often lined by a thick layer of atheromatous material. Most people who look at pathological material are agreed that thrombosis is not only a complication but a part of the atheromatous process, and this raises an interesting question. The incidence of disease of the coronary arteries has apparently risen greatly in the present century. In the Pathology Department at the Western Infirmary, for example, in 1940 3 per cent of deaths were due to myocardial infarction, a condition now found in 20 per cent of deaths. It would appear that some environmental factor is the cause of this. Morris (1951) in an excellent study has reviewed the necropsy records of the London Hospital and assessed the frequency and severity of the atheroma observed over a period of forty years by measuring the frequency with which calcification of the coronary arteries was found. (Calcification of the coronary arteries is probably almost exclusively atheromatous in origin.) There appears to have been no increase in severe atheroma of the coronary arteries in the London Hospital over a period of forty years, although the incidence of myocardial infarction has increased sevenfold. This suggests that the increased incidence of myocardial infarction may be due to some factor other than atheroma.

Aetiology of Atheroma

In discussing this there are two main groups of evidence we must examine. First are the factors—presumably local—which cause the lesions to be patchy. Several are recognized. (1) Thrombosis could cause patchy lesions. (2) The accumulation of atheromatous material round the opening of a branch vessel is well known; this may be due to shearing strain on the vessel with damage to its wall, but it is possible that this distribution of lesions could be accounted for by simple hydrodynamic factors such as turbulence which might lead to drop out of platelets and local thrombus formation (see Mustard *et al.*, 1962). (3) Damage to the media of an artery favours formation of an atheromatous patch on the overlying intima. In man the occurrence of severe atheroma in the intima of a syphilitic aorta has been mentioned and in experimental animals it has been shown that medial damage predisposes to intimal plaques at the site of damage (Constantinides *et al.*, 1958). (4) There is an interesting point about the localization of the disease in some human cases of atheroma. Moderately advanced atheromatous plaques may be present in the aorta, yet the branches may be completely free of atheroma, and this suggests that the structure or metabolism of these branch vessels is different from that of the

aorta. There is some evidence that the composition of fat which is present in atheromatous plaques varies in different vessels (Bottcher *et al.*, 1960).

General factors often require statistical methods for their investigation because of the co-existence of multiple aetiological factors. The difficulty of measuring atheroma tends to diminish the closeness of fit even when a true correlation exists. Bradford-Hill points out that if two occurrences are statistically correlated and if one is thought to be the cause of the other, then to establish cause and effect it must be shown that the cause operates before the effect, and external evidence shown which makes the suspected cause a plausible one.

(1) This has been done to some extent for dietary fat (Bronte-Stewart, 1958). It is known that ingestion of a diet rich in animal fat leads to an alteration in the serum lipids; also, that in populations who eat a lot of animal fat there is a very high incidence of myocardial infarction. Thirdly, people who have disorders which result in hypercholesterolaemia (e.g. diabetes and myxoedema) have a high incidence of myocardial infarction, and the disorder of fat metabolism precedes the development of myocardial infarction. These findings indicate that high dietary fat is a possible cause of atheroma. The evidence for plausibility comes from several sources. Fat is a very conspicuous feature of the atheromatous plaque and most experimental atheroma which has been produced is based on the feeding of some kind of fat (often with the use of tricks which will improve fat absorption, such as the administration of bile salts, or the administration of Thiouracil which impairs fat metabolism). Feeding experiments on animals have been criticized on the grounds that the lesions obtained are not identical to human atheroma, that the animals are overwhelmed with fat and have extremely high serum cholesterol levels and that most work has been done with rabbits which are vegetarians and not really suitable for this type of work. It remains to be seen whether modification of dietary habits in Western countries will cut down the incidence of myocardial infarction and other complications of atheroma.

(2) Of very considerable importance is the presence of high blood pressure. Morbid anatomical studies show that the systemic arteries are much more liable to atheroma than pulmonary arteries, but in patients with pulmonary hypertension pulmonary atheroma is often quite marked. Experimental hypertension in monkeys favours the development of atheroma (McGill *et al.*, 1961).

(3) An interesting general factor is the effect of exercise on the incidence of myocardial infarction. Morris *et al.* (1953) have shown clearly that people who have strenuous jobs have a much lower incidence of death from myocardial infarction than those who have sedentary occupations. In a study of bus conductors and drivers in London, he has shown that the conductors get more angina but less sudden death and less fatal myocardial infarction than the drivers. There are other factors which might operate here, but Morris

extended the survey to include postmen and sorting-clerks, with a similar result. Examination of death certificates also showed that people who have strenuous occupations have a lower mortality rate from myocardial infarction than their sedentary fellows and that this is not related to the social status of the occupation.

(4) Another possible general aetiological factor is cigarette smoking which influences death rates from ischaemic heart disease in an unknown way. Doll and Hill (1956) have shown a slightly increased mortality rate from ischaemic heart disease in heavy smokers in this country. The Americans find very striking increases in death from coronary artery disease with the number of cigarettes smoked, and the discrepancy between the two countries seems to be a real one; it may be due to the fact that many more Americans than British die of ischaemic heart disease. There is recent evidence suggesting that people who have given up smoking cigarettes have the same expectation of death from coronary artery disease as non-smokers (Doyle *et al.*, 1962).

It has been possible in the time available only to mention some of the difficulties of the problem of the pathology of atheroma. For real progress we must define atheroma more accurately, learn to measure it and its complications with more precision and find a more suitable experimental animal—one which is willing to sit around, smoke cigarettes, and eat a lot of animal fat. So far, man seems to be the only one willing to do this!

DISCUSSION

K. BLOOR (*Glasgow*):

I personally don't believe that cigarette smoking has got anything to do with arteriosclerosis at all. If you inspect the series of Hammond and Horn, Dorn and Doll and Bradford Hill, you will find that people who have given up smoking have a considerably higher death rate than would be expected if they had continued to smoke. This is commented on in all these series and the only explanation which is offered for this in each one is that these people presumably gave up smoking because they were already ill.

R. B. GOUDIE:

This is a great difficulty in studying atheroma. People produce conflicting evidence and it is extremely difficult to reach any conclusion. However, the association between cigarette smoking and ischaemic heart diseases, I think, is clearly established by most workers. The chance of dying of coronary artery disease is increased to a greater or lesser degree if you are a cigarette smoker—of course this may be due not to cigarette smoking but to the kind of person you are, which makes you both a myocardial infarct victim and a cigarette smoker. I introduced the subject of former smokers, doubtful as the evidence may be—because, if confirmed, it would constitute very good evidence that cigarette smoking is directly tied up with ischaemic heart disease if not with atheroma itself. I agree that it's not proven.

QUESTION:

Is it not a question of whether there is a correlation between smoking and coronary artery disease or smoking and the effects of coronary artery disease?

R. B. GOUDIE:

Yes. In an ideal situation you should get a perfect correlation between cause and effect. You don't get a perfect correlation when multiple real causal factors operate. A correlation

does not distinguish between possible direct causes or factors contributing indirectly. This is why we need a really satisfactory experimental animal so much.

QUESTION:

Can I ask about the rate of coronary disease in women? In the last forty years cigarette smoking in women has gone up so markedly there should be a definite rise in coronary disease in women?

R. B. GOUDIE:

There has been a marked increase in the occurrence of coronary artery disease in women, but I do not know if this is related to cigarette smoking or if the male : female ratio has changed.

W. FULTON (*Glasgow*):

I wonder if I might go back to the aspect of atherosclerosis which concerns most of us as clinicians—its prevention. What causes the thrombosis? We have to consider the aetiology of the disease in its origin and the aetiology of the complications. In my experience it is very common to find evidence of previous thrombosis below a fresh thrombus. The lesions complicated by thrombosis are in fact themselves thrombotically determined. Ulcerations of the atheromatous plaque and haemorrhage into the atheromatous plaque have been suggested as factors predisposing to thrombosis. Would Dr. Goudie agree that what has been described as degeneration is very often a phase in formation of a plaque from fibrin? I wonder if there is anything to suggest why thrombosis should take place on one plaque and not on another.

R. B. GOUDIE:

These are very interesting questions which I can't answer. Your observations are an important piece of evidence in favour of Duguid's theory, but although there are many possible causes for thrombosis we do not really know why thrombi form. We have looked at our own autopsy figures over the last 20 years during which there is a sixfold increase in death from myocardial infarction and have found that the incidence of recently formed thrombus in the coronary arteries has remained steady at 60 per cent. There appears to be no change in the relationship of coronary thrombosis to myocardial infarction: if the percentage of cases showing recent thrombosis had increased we might have had a clue to the answer of part of your question.

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THE ORIGIN AND SPREAD OF OCCLUSIONS OF THE FEMORAL AND POPLITEAL ARTERIES

J. KENNEDY WATT

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MR. BRANDON, ladies and gentlemen, it gives me great pleasure to return to Law where I spent many happy days and to see you, Sir, in the Chair at this session of what I am sure will be a very successful conference.

I wish to discuss the pattern of arterial occlusion in intermittent claudication, and to limit my remarks to the femoral and popliteal arteries. The material available consists of 264 patients with claudication, where aorto-iliac occlusion was absent and in whom bilateral femoral arteriography was performed. There are therefore 528 arteriograms available for analysis.

In the equipment used in Belvidere Hospital, the X-rays are shielded by a cone and the films placed on three trays in a cassette tunnel, the trays being removed manually as each film is exposed. Because of the tube distance which is fairly long at 50 in., there is relatively little distortion of the artery on film and as all the arteriograms were performed with this equipment and at the same tube distance, it seems feasible to compare films in different patients.

Arteriograms illustrate bilateral symmetrical occlusions in the adductor region with extensive development of collateral vessels. Most occlusions occur in this region and the X-ray exposure is arranged to show the details of this region. The region of the groin is under-exposed and the common femoral junction may be difficult to visualize or in some cases is not even included on the film. Accordingly, it is not possible to measure the arteries from the common femoral junction to the popliteal bifurcation and to relate the length of the occlusion to the total length of the artery. Because of this, I have chosen to measure occlusions on film from one point which is fixed, viz. the level of the knee joint.

If one measures occlusions from the level of the knee joint and charts them on graph paper, one obtains the record on the left-hand side of Fig. 1. Occlusions are drawn against a scale in which zero is recorded at the knee joint, and 40 cm is chosen to indicate the level of the common femoral junction. On 29 films on which I was able to measure the distance from the knee joint to the common femoral junction, the mean was 40·034 cm with a standard deviation of 1·5 cm. The popliteal bifurcation is recorded at minus 5 cm which was the mean and also the mode of 97 of the patients.