INTRODUCTION

Atherosclerosis consists of irregularly placed plaques arising in the inner intimal layer of arteries, containing lipid, smooth muscle, fibrous tissue and collagen. It occurs in arteries large and small, including the coronary arteries.

ARTERIAL VASOSPASM AND Atherosclerosis

One of the most striking observations in all the vast literature on coronary heart disease is the way any coronary vasospasm tends to occur focally within the coronary arteries and at sites already affected by atherosclerosis. On common-sense grounds, this was not at all what I would have expected studied the topic in the late 70s. I thought that the atherosclerotic plaque would surely impart a high degree of rigidity to the arterial segment concerned, so that these areas ought to be the last to constrict. Indeed, such an argument was often used in the past against any important role for vasospasm in the coronary circulation. It was argued that if arterial smooth muscle contraction occurred at all, it would only be likely to narrow relatively normal segments of the coronary artery, whereas the only place it would matter would be in the areas already splinted from its effects by atherosclerosis.

It has now been recognised that many atherosclerotic plaques are eccentrically placed rather than totally encircling the arterial lumen, so allowing that constriction of the remaining relatively normal cross-sectional arterial segment could indeed narrow the artery at that point. Even so, this still does not give an explanation for the curious juxtaposition between spasm and atherosclerosis. It occurred to me that the relationship might make a great deal more sense if we viewed it the other way around, i.e., the propensity of particular coronary artery segments to undergo spasm might, through many repeated episodes causing wall damage, and actually be the cause of the progressive atherosclerotic plaque itself. The present chapter will analyse this view in detail.

It has to be admitted at the outset that this is a perspective born more of a reversal of usual
ways of seeing than of any data synthesis along the lines I was at such pains to delineate in chapter 2. Nonetheless, before being allowed to see the light of day, it was made to address the outstanding problems of atherosclerosis research, and its acceptability as a theory will depend as much as anything else on how well it can explain these. In Popper's terms, any theory must account for as wide a body of evidence as possible before it can be given the status of a 'good' working hypothesis, and I hope to show that the present view offers a better explanation than existing theories in many of the difficult areas of atherosclerosis research.

In the 2nd edition of this book, I will, as far as I can, update the references, though I have to admit that my information may not be entirely up with the recent literature in this respect.

THE PATHOGENESIS OF ATHEROSCLEROSIS

Background

There is a vast amount of literature on the nature of atherosclerosis, and indeed much of plaque growth after initiation can now be explained as a response to injury by stimulation of smooth muscle cell proliferation in the arterial intima, including incorporation of various plasma factors such as low density lipoproteins, or LDL, and platelet factors. This 'modified' smooth muscle cell in the arterial intima (the myointimal cell) has achieved an increasing prominence in our understanding of the atherosclerotic lesion, and is now well-recognised to have secretory as well as contractile functions, with a capacity to change from the former to the latter after injury. This includes the multipotential capacity when stimulated to produce elastin, collagen, and a general increase in ground substance matrix, thereby being able to account for both the amount and variety of connective tissue elements within the atherosclerotic plaque. Much less is known about the early events in plaque evolution, but deliberate damage to the arterial endothelium experimentally does cause lesions closely akin to human atheroma, allowing plasma, monocytes, and other blood element insudation into the wall, with subsequent proliferation of modified smooth muscle cells and connective tissue within the intima, presumably under the influence of local platelet-, endothelium- and smooth muscle cell- derived growth factors. This damage need not have to be so severe as cause actual endothelial denudation, since the endothelium seems quite capable of releasing such growth factors under minimal stimulation.

So once a plaque is started artificially we can, even with present knowledge, give a reasonable account of its progress by reference to the proliferation of, and secretion from, the intimal smooth muscle cell under various influences. However, there remain several unexplained and very puzzling areas of plaque evolution in man. I now discuss these and, in doing so, use our four separate categories delineated in chapter 2 to dissect the information, namely the Anatomical, Pathological, functional and Aetiological sub-groups of diagnosis.
OUTSTANDING QUESTIONS IN ATHEROSCLEROTIC RESEARCH

The major questions are as follows:

1. **Anatomical.**
   Why is there such a patchy distribution of atherosclerosis over the arterial system in man, and why is the process largely confined to the intimal layer of the larger arteries?

2. **Pathological aspects.**
   How does the plaque commence, and if it is indeed initiated by damage to the endothelium, how is this brought about? Why does it appear to progress so episodically, and what is the relationship of atherosclerosis to the patchy superficial infiltrations of the aortic intima seen in the young? Do these fatty intimal arterial streaks and grey gelatinous intimal elevations etc. seen in surprisingly early childhood really represent the first signs of atherosclerosis and, if so, why do they seem so frequently to regress during early life?

3. **Functional considerations.**
   How are we to explain the poor clinico-pathological correlation between the extent of atherosclerosis, for example in the coronary arteries, and the degree of associated symptoms like angina, or the presence of the secondary changes of coronary thrombosis and myocardial infarction? There are sometimes huge discrepancies in this regard, with severe atherosclerosis being seen at times without any clinical symptoms at all, and at the other extreme, coronary thrombosis and myocardial infarction occurring in what appear to be completely normal coronary arteries. (See also chapter 5).

   There is another important question in this functional category. How are the complications of plaque haemorrhage, necrosis, liquefaction, calcification, and rupture brought about, and how do these complications relate to the ischaemic events with which they so frequently appear to be associated, e.g. plaque haemorrhage at the time of acute myocardial infarction in man?

4. **Aetiological questions**
   What are we to make of the Benditts' observation on the apparent monoclonal origin of the smooth muscle cells within individual human atherosclerotic plaques?

INITIATION OF THE ATHEROSCLEROTIC PLAQUE

The work of Ross and colleagues has shown that myointimal proliferation in the atherosclerotic plaque could well be a reaction to local endothelial damage. Just what might cause this local is very uncertain. It has always seemed likely that haemodynamic stress factors would be important, but under normal circumstances in man, it turns out that arterial blood flow is usually fairly laminar or non-turbulent, so that haemodynamic stresses due to flow are probably not normally high enough to cause appreciable arterial endothelial cell damage. Opportunities for alterations in wall stress forces from flow separation do arise in some areas, particularly at arterial branch points, but the anatomical distribution of atherosclerotic plaques cannot be explained entirely on this basis. Things might be very different, however, if active arterial constriction occurred with any frequency in vivo, particularly if it did so irregularly or focally along the arterial lengths, as often seems to be the case in the coronary arteries.
Let us therefore examine the possible haemodynamic consequences of focal arterial constrictions in vivo, and do so first in the area we know most about in terms of vasospasm, namely the coronary artery.

**ARTERIAL SPASM AND HAEMODYNAMIC STRESSES: THE CORONARY ARTERY**

We normally think of the Hagen-Poiseuille equation when trying to visualise blood flow haemodynamics within the circulation. According to this, any arterial constriction should cause an increase in resistance to flow proportionate to the fourth power of the vessel radius, so that blood volume flow should fall by the same amount, and blood flow velocity should decrease in proportion to the square of the radius. If this law were to apply in our situation, we can see for example that a halving of arterial radius would lead to a reduction of blood flow velocity by 75 per cent. However, the Hagen-Poiseuille equation is most applicable to long regular constrictions within uniform small-bore tubes, and may not be nearly so relevant in the general circulation. In particular, it will not be applicable to short focal coronary arterial constrictions. Flow does not even obey the Hagen-Poiseuille equation at the entrance to long uniform constrictions, nor do so until many pipe diameters down a narrowed length. Focal constrictions in coronary arteries are often only a few millimetres long, so the Hagen-Poiseuille equation will certainly not apply to these.

If flow does not obey the Hagen—Poiseuille equation in short arterial constrictions, what rules do apply? I suggest here that local blood volume flow in these circumstances may not change very much at all, so that Bernoulli’s law becomes applicable, whereby flow velocity will vary inversely with the square of the radius at the constricted site in exactly the opposite way to the predictions of the Hagen-Poiseuille equation. Now, the more the narrowing of the artery, the higher the blood flow velocity.

In vitro, increases in flow velocity certainly occur at a point of constriction where flow is being driven by constant pressure. This may be readily demonstrated by the simple experiment of gradually constricting the end of a garden hose with the finger. In vivo, blood flow circulation is auto-regulated, so that where the introduction of any local arterial constriction does tend to add a significant resistance to flow, compensatory relaxation of the arteriolar bed will tend to keep the overall resistance fairly constant. Hence blood flow might not fall at all, with the only change being a slight shift in the site of resistance from the distal arteriolar bed to the new arterial constriction. Under these circumstances, flow through the constricted arterial segment will not be just under constant pressure, but under constant flow, and hence will obey Bernoulli’s law quite closely, so that flow velocity will increase in inverse proportion to the square of the narrowing at the constricted point. Of course, with more severe constrictions, there will eventually come a time when both blood flow velocity and blood volume flow will fall, but this may not happen until the artery becomes very narrow indeed. Resistance being proportional to length, this will be particularly so with short segmental arterial constrictions. That situation is not unlike the one with cardiac valvular narrowing such as aortic stenosis, where a reduction in cross-sectional area of as much as 60% is needed before the narrowed area offers any appreciable resistance to flow. Even without auto-regulatory mechanisms, therefore, short localised constrictions have to be quite severe before noticeably altering blood volume flow. The overall effect of these factors will be to cause arterial blood flow velocity to increase in
inverse proportion to the square of the reduced radius at any focally constricted point, so causing endothelial damage at that point.

BLOOD FLOW VELOCITY AND WALL SHEARING STRESS

How will this increase in blood flow velocity affect shear stress on the arterial wall? One difficulty is that there are no simple equations for calculating arterial wall shear stress. Not only does it depend on flow velocity and the degree of turbulence, but also on the length of narrowed arterial segments. Fry has shown that haemodynamic endothelial stress is high both at a point just beyond the entrance to short experimental aortic stenoses, and again just beyond its point of exit.

Whatever the case, there is no doubt that arterial constriction can lead to endothelial damage at the constricted site. Moreover, Gertz’s studies give insight into the mechanisms involved in the initial stages of plaque formation. Following the induction of experimental arterial spasm in vivo, he observed a series of changes progressing from initial endothelial damage and desquamation of endothelial cells, to platelet attachment to the exposed subendothelial tissue, and eventual thrombus formation at the point of maximum constriction, all over as short a time as 15 minutes. Such platelet attachment may be relevant not only to that local thrombus formation which plays such a role in acute clinical events like myocardial infarction, but through the liberation of smooth muscle cell mitogens, may also be important myo-intimal cell change and proliferation so as to contribute to atherosclerotic plaque progression as well.

Of course, a single episode of arterial vasospasm would hardly cause enough damage enough to result in a full-blown atherosclerotic lesion. If arterial constriction were to be important, repeated episodes would be needed. But from the clinical evidence we have so far, repeated vasospasm may indeed occur, at least in the coronary artery, and go on to produce focal atherosclerosis. This was well demonstrated in a patient with Prinzmetal’s angina, initially due to reversible local vasospasm, who went on to develop a fixed atherosclerotic obstruction at the site of spasm over an 8-month period of recurrent chest pain. As a result, Marzilli and colleagues also recognised the possibility that vasospasm might be important in the pathogenesis of atherosclerosis. To the possible objection that Prinzmetal’s vasospastic form of angina is unusual, it should be said that lesser degrees of constriction also occur in other types of angina, and this could well have the same effect in the long run. Indeed, autoregulation of coronary blood flow might well determine that minor vasospastic events remained entirely subclinical early in the evolution of ischaemic heart disease, whilst nonetheless silently contributing to the gradual build-up of the atherosclerotic plaque.

Before leaving consideration of the relationship between coronary vasospasm and coronary atherosclerosis, we should ask which of the outstanding problems in coronary atherosclerosis could the current vasospastic theory actually explain?
CORONARY ATHEROSCLEROSIS AND VASOSPASM

1. Anatomical features.
   The patchy distribution of atheroma in the coronary artery would now be explained on the basis of the known tendency for vasospasm to occur focally or irregularly along the lengths of the coronary arteries.2,3,25

2. Pathological considerations.
   Minor repeated arterial constrictions could account for the gradual progression of atherosclerosis from repeated episodes of damage. This would explain the superficial fatty intimal streaks seen in childhood, and also why these lesions so frequently seem to regress during early life, whilst at the same time being the precursor for the development of the mature atherosclerotic lesion of the adult.16

3. Functional changes.
   The studies by Gertz showing endothelial damage and platelet adhesion during active focal arterial constriction31 give an indication of how coronary thrombosis might begin to build up at the site, whether superimposed on underlying atherosclerotic narrowing or not. Also, once any bout of vasospasm had passed there would be a tendency for any local thrombus to be either absorbed into the arterial wall at the site so as to contribute to the progress of the plaque.33

   Vasospasm might also explain atherosclerotic plaque complications. During growth, the plaque becomes vascularised from its base by vasa vasorum that grow in through the arterial smooth muscle coat from the outer adventitial layer.34 The plaque then becomes dependent on this blood supply for its viability, and this in itself could lead to a real difficulty. This is because any subsequent bout of active constriction of the main coronary artery medial coat at the site, sufficient to narrow the main lumen must, by definition, be generating a force high enough to overcome the prevailing coronary blood pressure. That being so, the pressure within the arterial wall itself, particularly towards the intimal layer, will be enough to cut off the intimal plaque’s vasa vasorum blood supply, so as to render it ischaemic. And if such constriction were severe or prolonged, the plaque could undergo ischaemic necrosis as a result. This could explain the plaque swelling, haemorrhage, and even rupture with superimposed thrombosis so often seen at the time of acute clinical events such as myocardial infarction18 and unstable angina.35 It might also account for the sudden onset of effort angina in some patients,36 through an abrupt increase in the degree of structural coronary artery narrowing.

   Another important point follows from this. Coronary artery media constriction could cut off the vasa vasorum blood supply without even producing any constriction of the main coronary lumen at all. This is because even before coronary medial smooth muscle contraction generates enough force to begin to narrow the main coronary lumen, that force will be sufficient to throttle the vasa vasorum blood supply running through it. In these circumstances, the plaque could be rendered ischaemic without any evidence of main coronary artery narrowing at all.

   An important question in this Functional category of diagnosis is how coronary arteries come constrict, so as to “behave like whimsical children” as Pickering once put it.36 The fact is that they do, as discussed in chapter 3, and it seems likely that alpha adrenergic sympathetic nervous stimulation is an important mediator.37,38 This is also suggested by the effect of the
alpha-adrenergic agent ergonovine \(^{39}\) to provoke coronary vasospasm in susceptible patients.\(^{40}\) Such evidence would fit with the current perspective of the underlying importance stress, through activation of the sympathetic nervous system: there is a known association of and psychological stresses and important ‘life events’ in the pathogenesis of the atherosclerotic plaque and its complications\(^{41}\). (See also Chapter 3.)

Many would agree that arterial vasospasm may occur in areas of atherosclerosis, but hold that this is of secondary rather than primary importance, most probably being related to a deficiency of endothelium derived smooth muscle relaxing factor (EDRF) at the site.\(^{42}\) This is of interest, but is not relevant to the \textit{initiation} of the atheromatous plaque.

4. Aetiological considerations.
The perspective taken here is that the all-important coronary artery constriction leading to atherosclerosis and its complications is driven by psychologial stress induced activation the sympathetic nervous system (see above).

ATHEROSCLEROSIS IN LARGER ARTERIES

One might argue that whatever the case in the coronary arteries, the distribution of atheroma is all wrong for it to be importantly related to vasospasm in any general way, because this disease is much more evident in the larger elastic arteries, such as the abdominal aorta, whereas it is the smaller muscular ones which are more prone to constrict. There are two facets to this question.

First, perhaps vasospasm is not the right word to apply to larger elastic arteries, for this term conjures up pictures of severe arterial narrowing, and most of the evidence suggests that this does not usually occur at this level. There is no doubt, however, that large arteries do have the capacity to constrict. They have a well-developed smooth muscle medial coat\(^{43}\) and are not at all the passive structures we once supposed. Even quite large arteries are well-supplied with sympathetic nerves through their adventitial coat,\(^{44}\) and despite the fact that these nerve fibres often end near the adventitio-medial border, they are able to influence a much wider area of the medial smooth muscle by indirect contraction coupling.\(^{45}\) We also know from experimental studies that quite large arteries are indeed able to constrict under sympathetic stimulation.\(^{46-48}\) This even includes the aorta,\(^{46}\) the rabbit thoracic aorta, for example, being one of the classical pharmacological preparations for studying vascular smooth muscle contraction.\(^{49}\)

It is true that the larger arteries have been traditionally thought to be relatively passive conduits of blood, but the evidence suggests that appreciable constriction may occur in some circumstances,\(^{50}\) particularly with stimulation of the sympathetic nerve supply.\(^{46,48,51}\)

Whatever the mechanism, it is known that chronic sympathetic nerve stimulation may not only cause arterial constriction, but with prolonged and repeated stimulation that this may result in experimental lesions closely resembling atherosclerosis. Thus, Gutstein and colleagues have shown that repetitive stimulation of the lesser splanchnic nerve in the rat leads eventually to experimental atherosclerosis in the lower abdominal aortic region supplied by this nerve.\(^{52}\) These workers went on to show that chronic stimulation of the hypothalamus in rats also
produces a similar but more generalised picture. These experiments bear importantly on the current vasospastic theory of atherosclerosis, both because acute vasoconstriction may lead to endothelial damage, and because prolonged artificial constriction experimentally can result in the formation of a local fibro-intimal plaque.

If the sympathetic nervous system is indeed important in mediating atherosclerosis, one might expect a relationship between this disease and psychological stress, and it is interesting in this regard that some investigators have shown that chronic experimental stress, be it physical or social, can result in the formation of experimental atheromatous lesions.

At the level of the larger arteries, even minor constrictions might lead to a relatively high shearing stress at the endothelial wall. Not only is basal blood flow velocity at its highest in the aorta, but the critical velocity for flow turbulence is greatest in vessels of largest diameter at any given velocity of flow, and these two factors probably take aortic flow quite close to turbulence even in normal circumstances. The stage would therefore seem set for quite minor constrictions to produce turbulent flow, particularly at any more narrowed points. Any decreased large artery compliance from an increase in its overall tone would also tend to reduce its capacity to accommodate each cardiac stroke volume, and this could add a further wall shear stress during systole. Finally, any constriction of small or large arteries doesn’t actually have to narrow the main arterial lumen before it can choke the plaque’s vasa vasorum blood supply and render it ischaemic/necrotic – as discussed above.

I suggest that episodes of focally increased arterial tone from sympathetic activation by psychological stress begin very early in life, and explain in consequence the grey gelatinous intimal elevations of early childhood and the fatty intimal aortic streaks of early adult life as the precursors of later atherosclerosis.

OTHER THEORIES ON THE AETIOLOGY AND PATHOGENESIS OFATHEROSCLEROSIS

Apart from the matter acceleration of atherosclerosis by high levels of cholesterol, there are really two major theories on its initiation.

The thrombotic theory.

This has a long history, having been given its first beginnings as Rokitansky’s "encrustation" theory in the 19th century. In more recent times Duiguid has pursued this. Essentially the theory holds that local platelet thrombi form on the arterial wall, and that this leads to the build-up of a local thrombus which then becomes incorporated into the intima as the atherosclerotic plaque. The present view does not challenge the importance of local platelet thrombi in helping mediate the progression of the atherosclerotic plaque - be it through thrombosis per se or platelet factors stimulating myo-intimal cell proliferation within the plaque - but it does question whether these thrombi form de novo, and I suggest that there must be some factor(s) localising the process, not only in anatomical space but also in time. The perspective taken in this chapter
is that this factor is episodic focal arterial constriction.

**The Benditts' View.**

The Benditts found an apparent monoclonal origin to the intimal smooth muscle cells in many human atherosclerotic plaques,\(^\text{19}\) and developed the view that plaques are in essence benign vascular smooth muscle tumours, occurring in response to agents that damage the arterial wall.\(^\text{58,59}\) There has been some controversy about this, not only in relation to the theory itself, but about the degree of monoclonality individual plaques actually show.\(^\text{60}\) However, let us for the moment accept the evidence on monoclonality and see whether it might have an alternative explanation. It is difficult, along the lines of the present vasospastic theory, to see how monoclonality could arise where arterial wall damage was severe enough to involve the media, as it frequently does in experimental atherosclerotic lesions.\(^\text{8}\) There, the smooth muscle cells involved seem to migrate from the medial layer to the intima,\(^\text{61}\) and in numbers far too large to support a monoclonal basis for any subsequent atherosclerotic plaque. But judged from the early fatty streaks, grey gelatinous intimal elevations etc. in the young \(^\text{16}\), damage in the human disease may be much more superficial, and this may mean that it is only the smooth muscle cells of the intima itself which are provoked to proliferate. Now, the "myo-intimal" cell is very sparsely distributed in the intima, at least in the newborn,\(^\text{8}\) so that local damage from constriction at any one point might initially stimulate only one such cell in early childhood, from which monoclonal origin the plaque could gradually evolve over the years, through repeated bouts of endothelial damage and its consequences.

**The Cholesterol story**

This is the main theory of our day. An association of atherosclerosis with high cholesterol was evident for many years up till the 1990s, but initial evidence on the effect of cholesterol lowering was controversial.\(^\text{62-64}\) The advent of the statins, however, clearly showed that theses agents could prevent heart attacks in patients with an elevated plasma cholesterol both in those with a prior myocardial infarction\(^\text{65,66}\) and those without.\(^\text{67}\)

Just how these statins work remains controversial. They do cause plaque regression to some extent, but at best, the magnitude of this regression correlates poorly with the quite marked reduction in clinical events.\(^\text{68}\) This is also the case with experimental atherosclerosis induced by cholesterol feeding,\(^\text{69}\) where it has been proposed the statins may exert their effects via changes in the vasa vasorum,\(^\text{70}\) in line with the present perspective. Others take the line that statins stabilise the plaque against complications such as fissuring and disruption.\(^\text{68}\) Improvement in endothelial function has also been invoked.\(^\text{71}\) Clearly, there is more to the story than gradual plaque build up from cholesterol deposition. For one, plaque size is a poor predictor of the site of any subsequently related myocardial infarction. For another, atherosclerosis in man tends to progress in an episodic way,\(^\text{72}\) probably linked to recurrent bouts of plaque complications.\(^\text{73}\) Such findings are consistent with the present vasospastic perspective that recurrent coronary artery vasospasm leads to episodic throttling of the plaque blood supply plaque, rendering it ischaemic or necrotic.

The statins have provided a significant contribution to the treatment and prevention of acute manifestations of cardiovascular disease. The jury is still out, though, on the pathogenetic
mechanism(s) underlying this.

CONCLUSION

This leads to a final point. It seems to me that one of the real positives for the current vasospastic theory of the origin of atherosclerosis is that it can explain a great deal more about the condition than it was originally put forward to do – both in respect to plaque progression and plaque complications. At the very least therefore, it should be considered as a good working hypothesis.

So much for our analysis and synthesis of theory. In the next chapter we shall look at the value of this vasospastic theory in explaining disease affecting various-sized arteries, and at how it might help understand the pathogenesis of vascular disease in different organs.
REFERENCES


