

## WHAT IS ATHEROSCLEROSIS?

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At first sight the answer to the question posed by the title of this essay is easy. It is a disease of medium sized and large arteries that may lead to occlusion, dilatation, aneurysm formation and rupture. Atherosclerotic lesions in smaller vessels such as the coronary, renal, mesenteric and cerebral arteries may also be associated with thrombosis brought about by rupture of plaques, platelet adherence and the whole coagulation sequence. It is a frequent cause of morbidity and mortality in the Western world and has been well recognised for centuries. Ancient Egyptians saw it in their corpses and it can still be found in mummies of that period. However the epidemic of ischaemic heart disease is a feature of the present century. Myocardial infarction was only recognised and clearly described in the first decade of this century. We are now faced with a widespread lethal disease largely confined to Homo-sapiens, other primates are rarely afflicted, and the explanation for this saturation is still not forthcoming. Nor do we have clear views about the early cellular events that occur in atherosclerosis and the factors that bring it about.

Ischaemic heart disease means different things to different people. The pathologist recognises it as atheromatous and thrombotic occlusion of coronary arteries associated with necrosis and fibrosis of the myocardium. Clinicians consider it to be a cause of angina pectoris, cardiac dysrhythmias and sudden death. However, these clinical conditions can occur without the presence of severe atheromatous coronary artery disease. In some cases of sudden death multiple platelet emboli in the small branches of the coronary tree may be the only findings.

Ischaemic heart disease is not therefore a single entity and a variety of risk factors are associated with it. Those that are well known are hyperlipidemias, hypertension, cigarette smoking, diabetes mellitus, obesity and lack of exercise. However when mortality indices are examined for different countries there are severe discrepancies between death from ischaemic heart disease and the presence of known risk factors in the population. A low

incidence in France and a high incidence in Scotland cannot be explained in terms of known risk factors. Only 50% of the differences can be accounted for in this way. Clearly other factors remain to be uncovered.

Experiments in animals have produced a confused picture about the aetiology of atherosclerotic disease. Early work in this century by Anitschkov and others showed the profound early effects of feeding cholesterol to rabbits. As little as 2% cholesterol in the diet produced massive collections of 'foam cells' in the intima of arteries. Some batches of rabbits responded more readily than others. The lesions were pure foam cells initially though a fibrous cap developed over them eventually. The nature of this lesion has been hotly debated and some say that they bear no relationship to the human disease. Furthermore Werthensen and others showed that totally purified cholesterol was ineffective when fed to rabbits and postulated that the oxidation products such as 35 oxysterols might be the disease producing agent. Comparable lesions have been produced in pigs, birds, non-human primates and other species by cholesterol feeding but the debate about the significance of these induced lesions in relation to human atherogenesis remains. The discovery of animals genetically predisposed to the development of atherosclerotic disease deflected views away from the cholesterol story to the importance of genetic factors. Studies of the white Carneau pigeon showed the presence of severe atherosclerosis which could be perpetuated by repeated inbreeding. Cross breeding with other strains of pigeon produced hybrids with less disease. Feeding cholesterol to the Carneau pigeon did not greatly enhance the development of disease.

The discovery of the Watanabe strain of rabbit indicated another possible atherogenic factor. These animals breed poorly and develop severe atherosclerotic disease. They pointed the way to the significance of lipoproteins in atherogenesis. Watanabe rabbits have a deficiency of lipoprotein receptors in their cells. They are incapable of dealing with beta-lipoproteins bearing cholesterol resulting in

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a persistent hypercholesterolaemia. Attention was therefore deflected from cholesterol itself towards the capacity of cells to deal with this sterol. Further investigations of the various lipoproteins revealed a possible protective effect of others. High density lipoproteins seem to be associated with a lesser tendency to develop atherosclerotic disease. Females have higher levels and this has been used to explain their relative freedom from atherosclerotic disease. This is supported by experimental evidence. Most non-human primates develop atherosclerotic disease when fed cholesterol; some such as the marmoset do not. This animal has high levels of high density lipoproteins compared to other primates.

Most of the lesions produced in experimental animals resemble the human fatty streak or spot seen in arteries of young people. This experimental work is also of doubtful significance because many dispute the notion that the fatty streak is an indication of early atherosclerotic disease. Fatty streaks occur in the thoracic aorta. Severe atherosclerosis occurs in the abdominal aorta. This discrepancy is the source of the argument. Another important point is that fatty streaks are mainly an aortic disease in the young whereas such lesions are rarely seen in the coronary arteries until the late teens. Coronary arteries of young people show diffuse and focal intimal fibromuscular hyperplasia with little lipid in them. If these represent early atherosclerotic disease the lipid has little part to play in their inception and other factors may be responsible.

Experimental studies of other factors such as **alloxan** induced diabetes, hypertension, cigarette **smoking**, exercise or lack of it, arterial injury by balloon catheters and the like have also produced confusing results. Hypertension and balloon injury produce **fibromuscular** lesions but experimental inhalation of cigarette smoke has never been shown to produce convincing arterial disease despite the strong epidemiological evidence in its favour. In the 1960's attempts to produce atherosclerosis in animals changed to those designed to prevent or reverse it. Some success was achieved by withdrawing cholesterol feeding and showing that lesions of the fatty streak type disappear. Armstrong and others showed this and even claimed that the fibrous component of the lesion could vanish as well. However most authors accept the reversibility of fatty streaks but not of more advanced lesions with a fibromuscular component.

The view became generally accepted that the atherosclerotic lesion was the response of the arterial wall to some form of injury. It was a reparative response similar to any repair process following tissue damage. **Gresham** and later Ross supported this view and proposed the dominant role of the smooth muscle cell which could be stimulated to proliferate by various growth factors and also by **beta-lipoproteins** themselves. Attention turned to the cellular components of the lesion and it was natural that the first to be considered was the endothelial cell at the reactive interface between plasma and the vessel wall. The key question was whether loss of endothelial integrity occurred as this would expose the underlying vessel wall to infiltration by cellular and chemical components of the blood.

Experimental studies denuding endothelium by fine catheters and balloons inserted into blood vessels produce variable results. The finer the catheter and the smaller the area of injury the quicker the break is repaired and lesions do not develop. Large areas of **denudation** lead to platelet and macrophage adhesion with subsequent smooth muscle proliferation. Paradoxically proliferation of smooth muscle cells is initiated by growth factors from endothelial cells which also are capable of producing collagen and elastin. The presence of endothelial gaps that might affect the permeability of the arterial wall has never been clearly demonstrated. This may be because of the capacity of endothelial cells to replicate rapidly and even to cover up endothelial cells about to be shed so that no breach in the surface ever occurs. Whilst endothelial cells have some capacity to contribute to atherosclerosis they have many properties that mitigate against it. They have anticoagulant properties and produce **prosta-cyclin** antagonists of platelet adherence.

Other cells must clearly be investigated as potential early atherogenic agents. Smooth muscle or myointimal cells as they have been called have long been considered the central cell in atherogenesis. When the vessel wall is injured they proliferate. Platelets are one of the possible injurious factors in this process. However for platelets to adhere endothelium must be breached. Platelets are interesting cells because of the **mitogenic** agents they produce that could cause smooth muscle cells to divide. However we have little evidence that platelets can be the initiators of atherosclerosis because we have no evidence of platelet adherence to undamaged endothelium.

Other **cells** can gain entry to the vessel wall and stimulate smooth muscle cell proliferation. For many years the monocyte-macrophage has been neglected despite the work of Duff and **Leary** in the '80's. These cells go into the intima, phagocytose debris and lipids and can easily pass out again into the vascular lumen. However if they ingest certain types of **lipid** such as oxysterols they die and liberate a variety of agents including a mitogenic factor stimulating smooth muscle cell growth.

Changes in endothelial cell permeability may **not be reflected in any morphological appearances**. Such changes of cell permeability or of intercellular permeability are well described in hypertension where agents such as Angiotensin **II** and other **vasoactive** substances affect permeability. Should this occur large proteins such as beta-lipoproteins enter the **wall. Here they are anchored by glycosaminoglycans**. Beta-lipoproteins stimulate smooth muscle **cell growth and may be the initiators of the atherosclerotic lesion**.

What then is atherosclerosis? Almost certainly it is the response of the vessel wall to injury. The nature of that injury is debatable. Other factors such as vascular allergy, virus infection and even monoclonal proliferation of cells induced by **oncogenic** agents need investigation. **When all that is done we probably shall still need to think again.**

#### SUGGESTED READING

1. Gresham **GA**. Atherosclerosis— **Controversial** aspects. *Hosp Update* 1986; 12: 765.
2. Gresham **GA**. Reversing Atherosclerosis. American Lecture Series, Charles C Thomas **Springfield**, 1980, pp 22.
3. Duff **GL**, McMillan **GC**, Ritchie **AC**. The morphology of early atherosclerotic lesions of the aorta demonstrated by the surface technique in rabbits fed cholesterol. *Am J Pathol* 1957; 33: 845.
4. Wolinsky **H**, Glagov **S**. Comparison of abdominal and thoracic aortic medial structure in mammals: deviation of man from the usual pattern. *Circ Res* 1969; 25: 677–86.
5. Gown **AM**, Tsukada **T**, Ross **R**. Human atherosclerosis: Immunocytochemical analysis of the cellular composition of human atherosclerotic lesions. *Am J Pathol* 1986; 125: 191–207.
6. Gresham **GA**. Primate Atherosclerosis. S Karger, 1976; pp 73.
7. Seifert **RA**, Schwartz **SM**, Bowen-Pope **DF**. Developmentally regulated production of platelet-derived growth factor-like molecules. *Nature* 1984; 311: 669–71.
8. Benditt **EP**, Gown **AM**. Atheroma: The artery wall and the environment. *Int Rev Exp Pathol* 1980; 21: 55–118.
9. Jaffe **EA**. Cell biology of endothelial cells. *Hum Pathol* 1987; 18: 234–9.
10. Reidy **MA**, Schwartz **SM**. Endothelial injury and regeneration. IV. Endotoxin: A non denuding injury to aortic endothelium. *Lab Invest* 1983; 48: 25–34.
11. Schwartz **CJ**, *et al.* Monocyte-macrophage participation in atherogenesis. Inflammatory components of pathogenesis. *Semin Thromb Hemost* 1986; 12: 79–86.
12. Gerrity **RG**, Goss **JA**. A monocyte chemotactic factor from the lesion-prone areas of swine aorta. *Circulation* 1983; 68: III–301.
13. Faggiotto **A**, Ross **R**, Harker **L**. Studies in hypercholesterolaemia in the **non-human** primate. I. Changes that lead to fatty streak formation. *Arteriosclerosis* 1984; 4: 323–40.
14. Reidy **MA**. A reassessment of endothelial injury and arterial lesion formation. *Lab Invest* 1985; 53: 513–20.