DEFINITION

1. In developed countries, occlusive vascular disease due to atherosclerosis and associated thromboembolic phenomena is the major cause of mortality and morbidity.

2. Atherosclerosis is the term applied to a focal condition of the intima (inner lining) of arteries associated with medial (middle coat) changes. The changes are widespread throughout the body, but differ in degree at different sites. In order, the coronary and cerebral arteries, the aorta and the arteries supplying the lower limbs are those most commonly affected.

3. Circulation of blood depends on a complex relationship between components of the blood vessel wall and of the flowing blood. In atherosclerosis we have an abnormal narrowed blood vessel wall causing reduced tissue perfusion. These altered walls also affect blood coagulation.

CLINICAL MANIFESTATIONS

4. Symptomatic arterial occlusion usually arises from stenosis of a segment of artery or from thrombosis occurring in a stenosed area. Haemorrhage into an atherosclerotic plaque, embolization of thrombotic material or spasm of a diseased vessel may also be involved.

CORONARY ARTERIES

5. Atherosclerosis of the coronary arteries results in reduced coronary blood flow and a discrepancy between the supply of and the demand for oxygen by the heart muscle. This causes **ischaemic heart disease or myocardial ischaemia**. Clinically, the resultant chest pain or tightness is **angina**.

6. If the coronary artery lumen is totally occluded, the resultant tissue necrosis of heart muscle supplied is **myocardial infarction,** commonly known as a "heart attack" or "coronary". The terms myocardial infarction and coronary thrombosis are often used synonymously although tissue infarction may occur without thrombosis.

CEREBRAL ARTERIES

7. Several syndromes arise from atherosclerosis of the cerebral arteries. In most developed countries cerebrovascular disease is the third most common cause of death after ischaemic heart disease and cancer. It is the cause of much physical and mental disablement in the elderly.

8. **Cerebral ischaemia** refers to impairment of function of the brain as a result of diminution in its blood supply. If ischaemia is prolonged or severe infarction will result. This will be particularly likely if the collateral supply to the ischaemic area is inadequate. The clinical pattern is of insidious mental and physical change with stepwise progression punctuated by minor acute episodes. If ischaemia is less prolonged or momentary a **transient ischaemic attack** may result. By definition such attacks cause symptoms for less than 24 hours. They are most frequently due to atheromatous thromboembolism. 20% have a cardiac source of embolism and about 5% are due to a rare type of arterial disease.

9. **Cerebrovascular accident (CVA) or stroke** includes both cerebral infarction (80%) due to embolism or thrombosis and haemorrhage (10%). It is not always possible to distinguish between these on clinical grounds. A cerebrovascular accident is usually of sudden onset and characterised by hemiplegia (paralysis of one side of the body). A quarter of strokes occur below age 65 years and half below age 75 years.

10. **Cerebral infarction** is necrosis of a portion of the brain, through occlusion of one of its larger arteries as a result of embolism or thrombosis. Infarction may occur without occlusion, when cerebral tissue inadequately perfused for a prolonged period undergoes softening.

11. **Cerebral haemorrhage** (spontaneous intracranial haemorrhage) occurs when an intracranial artery ruptures with extravasation of blood into the surrounding brain substance. This condition is commonly associated with hypertensive vascular disease.

12. **Cerebrovascular** accidents may arise from causes other than atherosclerotic occlusive vascular disease. These include head injuries, tumour, meningitis, drug or alcohol abuse, encephalitis, rheumatic heart disease, leukaemia, purpura and polycythemia.

PERIPHERAL ARTERIES

13. Peripheral vascular disease has increased in incidence in recent years and is particularly associated with ageing. A major causal factor is smoking.

14. The main arteries supplying the lower limbs are the sites most commonly affected. Occasionally the proximal arteries of the upper limbs are involved. Narrowing and progressive obliteration of the affected arteries occur and the clinical manifestations arise from ischaemia of the limb or limbs involved. The characteristic symptoms of peripheral atherosclerosis of the lower limbs is a cramp-like pain in the calf or thigh brought on by walking and relieved by rest, known as **intermittent claudication**.

15. Other features include coldness, numbness, paraesthesia and colour changes of the affected limbs. As the disease progresses, **pain at rest** may occur, usually at night, involving the distal portion of the feet and toes. Trophic changes may arise and include atrophy of the skin, deformity of the toenails, ulceration and **gangrene**. Involvement of the upper limbs gives rise to pain, numbness and blanching of the fingers but gangrene is rare.

ATHEROSCLEROSIS OF THE AORTA

16. Fatty streaks are visible in the aortas of children who die as young as three years. Clinical manifestations of aortic disease are however seen mainly in the elderly.

17. The typical lesions of atherosclerosis are first seen in the lower aorta. The enlarging vessel wall protrudes into the aortic lumen causing vessel occlusion. At the same time expansion occurs into the media leading to dilatation and aneurysm. The clinical presentation of an aneurysm is distinct from occlusive vascular disease.

18. The commonest aneurysm presenting to the clinician is **abdominal aortic aneurysm**. There are three common clinical presentations: -

    I. A **ruptured** or leaking aneurysm presents classically with pain, hypotension and a pulsatile mass in the abdomen.

    II. With **symptomatic** or expanding aneurysm, the patient presents with epigastric or back pain and on examination is found to have a pulsatile mass.

    III. An aneurysm may be **silent**, being detected on fortuitous X-ray or abdominal examination.

19. **Thoracic aneurysm** was formerly commonly due to syphilis. Today it is most likely to be due to atherosclerosis. In a few cases an aneurysm is caused by severe trauma to the chest involving the aorta. Thoracic aneurysms are usually asymptomatic but they may present with sudden death when rupture occurs. If symptoms do occur, these include chest pain and obstructive features due to pressure on the oesophagus, trachea or superior vena cava. Cardiac symptoms, mainly angina, may result if the aortic valve or coronary arteries are obstructed.

AETIOLOGY

20. The precise steps in the pathogenesis of atherosclerosis remain active areas of research. Some studies have been based on morbid anatomy, others on the epidemiology of atherosclerosis and, more recently, there has been a focus on the cellular biology of the arterial wall. Atherosclerosis progresses insidiously for many years before symptoms develop, making it difficult to follow the early development of disease in individual patients and to relate causally the several types of lesion that have been described. In addition, pathological studies show that the disease process is not relentless, but in the majority of cases proceeds by a succession of relapses and remissions.

The pathogenesis of atherosclerosis

21. The normal arterial wall consists of three layers. The innermost layer or **intima**, bounded peripherally by the internal elastic lamina, is a relatively empty space containing extracellular connective tissue matrix and, in children, an occasional smooth muscle cell. With increasing age there is an accumulation of both smooth muscle cells and extracellular matrix components. The **media** or middle layer of the normal muscular artery is composed of spirals of smooth muscle cells with surrounding collagen, elastic fibres and proteoglycans. The external elastic lamina separates the media from the outer layer or **adventitia**. The adventitia is made up of fibroblasts, smooth muscle cells and surrounding collagen and proteoglycans.

22. In atherosclerotic arteries the major changes are in the intima. These are considered to be the results of intimal injury. Characteristic lesions have been identified, namely **fatty streaks, fibrous plaques** and the **complicated lesion**. The **fatty streak** is characterised by a focal accumulation of smooth muscle cells which contains and is surrounded by lipid deposits. It causes no clinical symptoms. These lesions develop at different ages in different parts of the arterial tree but they are present in the aorta of virtually every child, regardless of age, sex or environment, from the age of 10 years. From then until the age of 25 years the extent of the aortic intimal surface covered by fatty streaks increases to 30-50%. The lipids found within the smooth muscle cells are cholesterol and cholesteryl esters.

23. The transition from fatty streak to **advanced plaque** begins with formation of a **transitional plaque** where there is extracellular lipid in the intima. Smooth muscle then proliferates and surrounds the lipid and produces increasing amounts of collagen. This is an **advanced** or **raised fibrolipid plaque**. By the third decade advanced plaques are common in Western countries.

24. The final transition is to an **unstable plaque** complicated by thrombosis. If there is no lipid core but a preponderance of smooth muscle cells, we have a **solid fibrous plaque**. A further variant contains many foam cells and is described as **gelatinous**.

25. In any one individual there will be a combination of plaque types. The advanced plaque or raised fibrolipid form must be present for symptoms.

26. Plaque development is slow and intermittent. Progression is due to the appearance of new lesions rather than the growth of pre-existing lesions. Thrombosis in plaques occurs following superficial intimal injury and the resultant thrombus adheres to the plaque surface. The thrombus may fill the lumen or it might break off, form an embolus and impact on a smaller more distal vessel. If deep intimal injury occurs, blood enters the plaque via the cap. The lipid inside is thrombogenic and so thrombus forms within the plaque.

27. Associated with the atheroma process is a disturbance of vascular tone so that vasoconstriction may be paradoxically induced leading to further reduction of blood low. In older people where atherosclerosis of the aorta is accompanied by the age changes of the aorta and often by hypertensive change, aneurysms may develop.

28. The evidence is that these processes go on all the time. In superficial thrombosis, spontaneous lysis due to plasminogen activation is taking place at the same time. Plasminogen activation also arises from intimal injury. The repair processes in deep injury are more complex and revascularization and fibrosis are involved.

Epidemiological studies of risk factors

29. Atherosclerosis results from the interaction of multiple factors. Risk factors are factors associated with an increased incidence of a condition. The association need not be directly causal. If a risk factor is identified, further study is required to determine whether it is independent of other factors. Risk factors may be inborn or acquired.

30. In Western populations the three major independent risk factors for ischaemic heart disease are high serum cholesterol, tobacco smoking and raised blood pressure. These account for half the variation in ischaemic heart disease incidence.

31. Serum cholesterol varies relatively little within a single population and in countries with low serum cholesterol ischaemic heart disease is uncommon. In Japan, where there is a high level of hypertension and smoking and low community cholesterol, the incidence of ischaemic heart disease is low. Within countries where overall community cholesterol concentration is low, the expected relationship at an individual level between ischaemic events and cholesterol level is seen.

32. There are wide international differences in disease incidence and in recent years, while disease has been declining in some populations, it has been increasing in others. Most of the studies on the risk factors for atherosclerosis have been done in relation to ischaemic heart disease in males aged 40-59 years. This should be borne in mind when considering atherosclerosis in the elderly, or non-cardiac manifestations of atherosclerosis. There may be differences in the significance of risk factors dependent on the part of the circulation affected.

    The following risk factors have been identified: **-**

AGE

33. The incidence and mortality of ischaemic heart disease increase with age. In men there is about a 15-fold increase in mortality between 35 and 44 years and 55 and 64 years. In females the increase is 30-fold. By the fourth decade of life ischaemic heart disease is the leading cause of death in males.

Perinatal factors

34. Recent research suggests that environmental influences in early life may be important in the later risk of coronary heart disease. Birth weight and weight at one year in males born between 1911 and 1930 are related to subsequent mortality from coronary heart disease.

35. The standardised mortality rate (SMR) fell from 111 in men who weighed 8.2kg or less at one year to 42 in those who weighed 12.3kg or more. Further studies suggest a similar link with adult blood cholesterol levels and risk of diabetes.

The heart and ageing

36. It is always difficult to differentiate between the inevitable effect of ageing and the coincident development of age-related pathology. In cardiac disease in developed countries this is particularly difficult because of the universal presence of atherosclerosis in elderly subjects. The ageing process itself leads to changes in the cardiovascular system. These in turn affect susceptibility to and manifestations of cardiac disease.

37. With normal ageing, myocytes decrease in number, but those remaining increase in mass. Interstitial collagen, fat and lipofuscin accumulate in the myocytes also occurs. In the very old amyloid is found in the myocytes.

38. Changes also take place in the heart valves. Aortic sclerosis and mitral incompetence commonly result and 10% of people over 80 years have floppy mitral valves.

39. Physiological changes in the elderly include less responsive heart rate, reduced resting left ventricular output and changes in the aorta causing an increase in left ventricular impedance. With increasing age, myocardial relaxation is prolonged, requires more energy and extends diastolic filling. Due to increased pressure in the chambers of the heart, there is increased likelihood of atrial fibrillation. Blood pressure rises with age regardless of hypertension. Renal blood flow reduces with age in the normal subject and there is an associated decline in renal function. There is also change in autonomic control of blood pressure, the sensitivity of the baroreceptors and in sensitivity to the various neuroendocrine substances involved in cardiovascular regulation.

40. Epidemiological studies of risk factors in atherosclerosis in the elderly have been limited but elevated systolic blood pressure, serum triglyceride and diabetes are considered particularly important.

SEX

41. Women have a lower incidence of atherosclerosis than men do. This is thought to relate to hormone factors as the difference diminishes around the menopause. Other factors which may be involved are distribution of body fat and the, until recently, different smoking habits of women.

RACE

42. No racial group is immune to ischaemic heart disease. In the UK, Asian immigrants have a higher risk than people born in the UK. This could relate to the high prevalence of diabetes.

FAMILY HISTORY

43. It has long been noted that atherosclerosis, particularly ischaemic heart disease, runs in families and a family history especially at a young age is an independent risk factor.

BLOOD LIPIDS

44. Serum total cholesterol is a simple predictor of blood lipid in both communities and individuals within the communities. Cholesterol is carried in the blood by lipoproteins Five major classes of lipoprotein are recognised. These are short chylomicrons, very low-density lipoproteins, (VLDL), intermediate density lipoproteins, (IDL), low density lipoproteins, (LDL), and high-density lipoproteins, (HDL). Two thirds of cholesterol is carried in low-density lipoproteins, (LDL) and about a quarter in high-density lipoproteins, (HDL). Very low-density lipoproteins, (VLDL), carries triglyceride. Some abnormalities of lipoproteins occur which are familial.

45. Reflecting dietary habits, the total serum cholesterol level within countries does not vary as much as between countries. In relation to atherosclerotic events a rise in cholesterol is associated with a rise in incidence and deaths from ischaemic heart disease. However if total mortality from all causes is plotted against cholesterol level a U-shaped curve is obtained. There is an inverse relation between cholesterol and death from some cancers, trauma, respiratory disease and digestive diseases.

46. In the elderly, cholesterol and stroke are inversely related and results on the relation between cholesterol level and coronary heart disease are conflicting. These uncertainties mean that there is at present no general policy to measure and lower cholesterol levels in the elderly.

TRIGLYCERIDES

47. High fasting triglyceride levels have been implicated as a risk factor in ischaemic heart disease. As serum triglyceride tends to parallel serum cholesterol it is difficult to assess the true significance of triglycerides. The level may be of more predictive importance in women than men and in the elderly.

LIPOPROTEIN (A)

48. An individual's lipoprotein concentration is genetically determined, the substance being found in serum and in arterial walls. Scandinavian studies suggest that it is a independent risk factor for ischaemic heart disease. There is evidence that it may be a link between atherogenesis and thrombosis as it is homologous with plasminogen.

DIETARY FACTORS

49. The relation between diet and ischaemic heart disease has attracted much attention over the years. Man does not eat cholesterol or trigycleride but food. Many elements of the Western diet have been identified as possibly associated with ischaemic heart disease. These include saturated fat intake, fibre, salt, alcohol, coffee and vitamins which are antioxidants. Saturated fat intake is now considered the single most important determinant of serum cholesterol. It is not possible to show a close relation between an individual's diet and his individual risk of ischaemic heart disease.

50. The Mediterranean diet, high in Olive Oil is cardioprotective and studies in Eskimos where there is high fat intake from fish have shown an inverse relation between fish intake and cardiac mortality. The precise explanation remains unclear. Oily fish contain unsaturated fats which may act via triglyceride. Studies in animals suggest that the fish effect occurs whether the diet replaces meat with fish or whether fish oils are added as a supplement to a meat-based diet.

BLOOD PRESSURE

51. Risk of ischaemic heart disease is related to increasing levels of diastolic or systolic blood pressure in a direct and continuous manner. It is also known that in countries where serum cholesterol is low this effect is less.

52. Where blood pressure is treated, recent overview of 14 trials showed that there will be a reduction in stroke incidence but not in ischaemic heart disease. This is particularly so in elderly subjects. A precise explanation is not yet forthcoming but it may be that metabolic abnormalities associated with high blood pressure or its drug treatment are involved.

TOBACCO

53. An association between tobacco use and ischaemic heart disease has long been recognised. The risk between cigarette smoking and myocardial infarction and sudden cardiac death is particularly strong. Pipe and cheroot smoking without inhalation have a less strong association. It is thought that smoking acts through its effect on fibrinogen. In patients who have had a myocardial infarction stopping smoking is accompanied by a reduction of 40% in infarct recurrence and mortality.

DIABETES MELLITUS

54. In countries where ischaemic heart disease is common the presence of diabetes mellitus increases the relative risk of ischaemic heart disease by twice or more in men and even more in women. In women the presence of diabetes seems to remove the natural female protection. Diabetes is an independent risk factor and at any level of the other risk factors the presence of diabetes more than doubles the risk. The precise mechanism of the diabetic effect is not known. It is thought to be brought about by lipid abnormalities probably through insulin.

OBESITY

55. Investigation of the association of obesity and ischaemic heart disease has produced discrepant results. This may relate to the different prevalence of obesity in different societies and sexes. It is not established whether obesity is an independent risk factor. Obesity may be involved through its association with diabetes, abnormal lipid metabolism, blood pressure and fibrinogen levels.

PHYSICAL ACTIVITY

56. The relation between physical activity and ischaemic heart disease has been the subject of much interest. Most studies have looked at males of middle age and who have sustained an ischaemic event. Like obesity, physical activity is associated with other life style factors such as diet and eating habits, tobacco smoking and alcohol consumption.

57. In the Seven Countries Study, 1200 men in the US, Japan, Sweden, Yugoslavia, Finland, Italy, the Netherlands and Greece were followed between 1957 and 1964. Those subjects who had the highest incidence of ischaemic events were lumbermen and farmers who had high levels of physical activity.

58. A well-controlled Swedish cohort study followed for a long time showed a negative correlation between activity at work and at leisure. High leisure activity protected against ischaemic heart disease but not work activity. When multivariate analysis was applied to the data, physical activity was not significant.

59. There is some suggestion from prospective studies that inactivity may increase the incidence of ischaemic heart disease compared with the physically active control. However, if blood pressure, cholesterol, smoking etc are controlled the association between physical activity and ischaemic heart disease disappears.

60. It is also important to note that all these studies relate not to mobility but to physical energy expenditure. The quality and amount of exercise may be very important. Morris in his civil service studies showed that only vigorous leisure time activity had any effect.

61. Exercise and ischaemic heart disease studies have looked mainly at young or middle aged men. The type of energy expenditure likely to be cardioprotective much exceeds that of which normal elderly persons would be capable. It therefore remains to be shown whether exercise is indeed cardioprotective, whether the effect is direct or via other factors and whether it is relevant in the old.

ALCOHOL

62. Alcohol and ischaemic heart disease have been shown to have either a negative or a U-shaped relationship with ischaemic heart disease. Present evidence indicates that moderate alcohol consumption is associated with a decreased morbidity and mortality from ischaemic heart disease. The effect may be mediated via increased high-density level cholesterol, increased fibrinolysis or antioxidant levels.

COFFEE

63. Studies on this are conflicting. The effect is mediated via cholesterol level. It is now generally agreed that the method of coffee preparation is important. Instant and filtered coffee, confer no risk on cholesterol level while boiled coffee (the preferred method in Scandinavia) leads to increased levels.

SEX HORMONES

64. Women are protected against ischaemic heart disease. This seems to be due to menstruation not sex hormones per se. Oral contraceptive use in women with other risk factors is associated with increased risk. The use of HRT reduces ischaemic heart disease events.

SOCIAL AND PSYCHOSOCIAL FACTORS

ETHNIC DIFFERENCES

65. There is a marked difference in rates of ischaemic heart disease in different countries and the rates change when people migrate. Broadly, immediately following migration when people remain in ghettos the rates remain similar to the rate in the home country.

SOCIO-ECONOMIC FACTORS

66. Ischaemic heart disease is more common in wealthy countries than in poor and in the past the rate of ischaemic heart disease was higher in the higher status groups. This observation led to the popular belief that ischaemic heart disease and psychosocial stress are associated with the executive lifestyle.

67. To demonstrate such a postulate by reliable evidence is difficult. Obvious questions include: -

    What is psychosocial stress?

    How is it to be measured?

    How do we reproduce it artificially in a way which is reproducible and related to real life?

68. Many of the studies looking at stress and ischaemic heart disease are poorly designed with inadequate case numbers, poorly selected controls and ill defined outcomes. There is much reliance on retrospective subjective opinion or questionnaires and most studies have involved individuals who have already sustained a clinical atherosclerotic event.

69. In prospective and angiography studies, marital status and other family circumstances have not been associated with ischaemic heart disease. Very traumatic experiences such as bereavement and disaster may precipitate a temporary increase in risk.

70. Since the 1950s the rate of ischaemic heart disease has been increasing in working class men and in the 1960s overtook the rate in the upper classes. At the same time the absolute rate in the non-manual occupation classes has been declining. Within the non-manual group another gradient is seen. The Whitehall study of UK civil servants shows that the higher the job grade the lower the mortality from ischaemic heart disease.

71. Explanation of these findings in relation to ischaemic heart disease and occupation is not yet available. There are many possible influences. These include higher smoking rate in lower social groups; different diets - not more fat but less fruit and vegetables: more obesity; higher mean blood pressure; less leisure time activity but not less overall physical activity.

72. Some studies have looked at personality type or behaviour pattern and longitudinal American studies supported the view that ischaemic heart disease was found in individuals described as striving, ambitious, restless and excessively concerned with time and deadlines. Results have now emerged from similar studies conducted in Europeans which do not bear out these findings.

73. It is well documented that during the Second World War and shortly after the people of Western Europe were more healthy than at any other time this century. Incidence of ischaemic heart disease was low and male life expectancy increased by more than 2 years over the period 1940-50. By contrast in post Cold War Eastern Europe the incidence of ischaemic heart disease is increasing.

74. A possible explanation for these observations has been informed by recent behavioural studies in primates. Pathological studies of baboons and macaques have demonstrated differing progression rates of atherosclerosis and its acute manifestations in individual animals dependent on their acceptance and position within the social group. These findings suggest that social support may influence the progress of human atherosclerosis and its acute manifestations. Where people form groups with common interests, tasks or motivations atherosclerosis has low incidence.

75. The current British authoritative view is that the overall evidence does not show a causal association between psychosocial stress and the atherosclerotic process. Where an acute cardiac manifestation of atherosclerosis occurs in close time relation to an acute stress incident, physical or psychological, it may not be possible to dissociate the two. Present evidence does not show an association between acute stress (physical or mental) and cerebral infarction or haemorrhage or peripheral embolism.

CONCLUSION

76. Atherosclerosis is a constitutionally determined disease of the arteries which begins in the early years of life. The pathological process is well established in childhood and follows a variable course thereafter. Certain risk factors may accelerate the progress of the disease. The likelihood of clinical manifestations of atherosclerosis is increased in the presence of such aggravating factors, which are synergistic in effect.

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