

**PROBLEM SOLVING EXERCISES – ATHEROSCLEROSIS & CARDIOVASCULAR DISEASE**

**PSE: PART I: ATHEROSCLEROSIS**

**AIM**

To understand the nature and factors influencing development and progression of atherosclerosis.

**ATHEROSCLEROSIS: INTRODUCTION**

One of the most common causes of death in the Western world is due to the consequences of coronary artery disease including myocardial ischaemia and myocardial infarction. This most often results from atherosclerosis in the coronary arteries. The process of atherosclerosis leads to formation of atherosclerotic **plaques**, which have a **fibrous cap** overlying a soft centre, composed of lipid and necrotic material (**lipid pool**). Atherosclerotic plaques may rupture, stimulating the development of thrombus. A large thrombus on the surface of a ruptured plaque can cause obstruction of the lumen of the artery – and this is the commonest cause of myocardial infarction. Spasm of the coronary arteries and emboli in the coronary arteries are occasionally involved, but less frequently. To prevent atherosclerosis, it is important to understand the underlying processes (see diagram below) and the relevant risk factors.

**Risk factors for atherosclerosis include: 4 major risk factors - smoking, hypertension, diabetes mellitus, hyperlipidaemia**, and several minor risk factors - increasing age, male sex (hormonal effects on blood lipid levels), family history, obesity, & certain ethnic origins.

The **AORTA** and larger arteries are **elastic** arteries. Arteries have 3 layers: tunica intima (inner layer in contact with blood in the lumen), tunica media (middle layer containing smooth muscle cells), and tunica adventitia (outer layer composed of supporting fibroconnective tissue with capillaries and nerves). The 3 layers are separated by 2 elastic laminae. In H&E sections, the elastic laminae appear pink and usually have a wavy appearance. The **intima** is the innermost layer and lies between the innermost elastic lamina and the endothelium. At birth the intima consists solely of the endothelium with its basement membrane. Within the arterial system including the aorta and the coronary arteries, there is uniform thickening by smooth muscle cells and fibrous tissue, to form so-called **diffuse intimal thickening (DIT)**.

**ATHEROSCLEROSIS: PROBLEM-SOLVING EXERCISE**

First, look at the photographs of **macroscopic specimens** of normal aorta (P22.1) and atherosclerotic aorta (P22.2), then examine the photomicrographs of **microscope slides** of normal aorta (P22.3) and an atherosclerotic plaque (P22.4) taken from atherosclerotic aorta. Proceed to the **diagram** of atherogenesis and answer the **problem-solving questions** about this pathological process.

**PHOTOGRAPHS: MACROSCOPIC SPECIMENS:**

**P22.1** Normal Aorta

Catalogue Number	Small Image	Image Map	Large Image
N_CR_AO_17.jpg	<a href="#">Normal Aorta</a>		<a href="#">Normal Aorta</a>

**P22.2** Atherosclerotic Aorta

Catalogue Number	Small Image	Image Map	Large Image
A_VA_AZ_AO_41.jpg	<a href="#">Atherosclerotic aorta</a>		<a href="#">Atherosclerotic aorta</a>

## PHOTOMICROGRAPHS:

### P22.3 Elastic artery: normal aorta

Catalogue Number	Small Image	Image Map	Large Image
N_CR_AO_18.jpg	<a href="#">Elastic artery – normal aorta</a>		<a href="#">Elastic artery – normal aorta</a>

This aorta was from an 18-year-old girl killed in a road traffic accident.

### P22.4 Aorta : atherosclerosis complicated by thrombosis

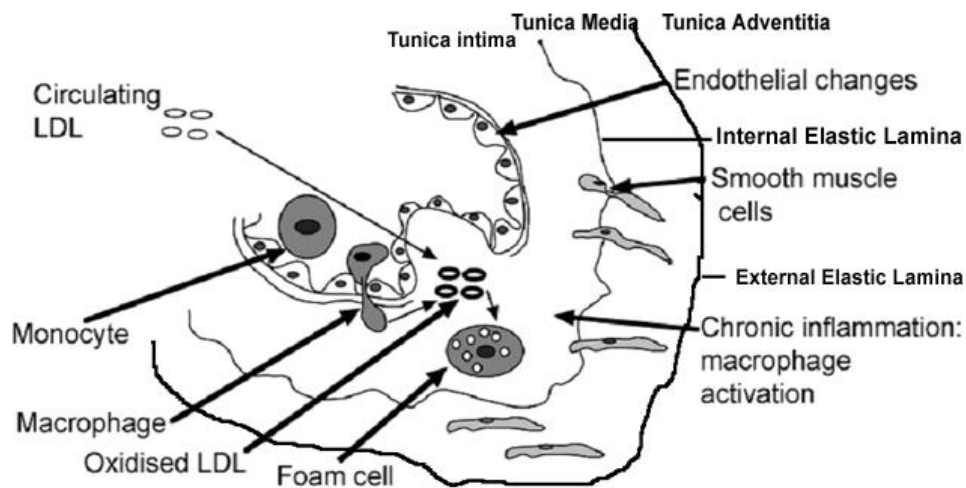
Catalogue Number	Small Image	Image Map	Large Image
A_VA_AZ_AO_42.jpg	<a href="#">Aorta : atherosclerosis</a>		<a href="#">Aorta : atherosclerosis</a>

This aortic tissue is from an 80-year-old man who had thrombosis over plaques in his abdominal aorta.

**Thrombus** has formed over the **ruptured surface** of an atherosclerotic plaque containing abundant lipid. Within the plaque, there are clear central areas which originally contained **necrotic tissue** and **lipid**, (the latter dissolved out during the processing of the tissue), covered **by a fibrous cap**. In fresh tissue, the necrotic centre of these lesions is very soft with a fancied resemblance to porridge, hence the lesion is called **atheroma** (from the Greek word, athera = gruel). The central necrotic material contains many **cholesterol clefts** (crystal-like formations of cholesterol that dissolve out during tissue processing).

Macrophages are present within the plaque, whose cytoplasm is filled with many lipid-laden vacuoles. These appear after tissue processing as clusters of clear bubbles, hence the descriptive term "foam cells".

**This DIAGRAM OF ATHEROGENESIS shows the major components important in the formation of an atherosclerotic plaque and its progression.**



Monocytes (in blood) enter the Tunica Intima becoming macrophages and these take up the LDLs and lipid to become Foam cells/Foamy macrophages.

**ATHEROSCLEROSIS: PROBLEM-SOLVING QUESTIONS:**

- QA. At the earliest stages of plaque development, what influences lipid circulating in the blood, in the form of **Low Density Lipoprotein (LDL)**, to enter the tunica intima of the artery wall?
- QB. What stimulates blood **monocytes** to enter the arterial wall (becoming tissue macrophages) at the same site as the LDL?
- QC. If the macrophages can phagocytose LDL forming "foam cells" (containing intracellular lipid), how does the **extracellular lipid pool** form and grow larger? (seen as cholesterol crystals and lipid gruel in your section).
- QD. What triggers the **smooth muscle cells** in the tunica media to migrate to the tunica intima, proliferate and secrete extracellular matrix?
- QE. Can you assign the four major risk factors (**smoking, hypertension, diabetes mellitus & hyperlipidaemia**) to pathogenic events in atherosclerosis?
- QF. What makes an atherosclerotic plaque **rupture**? Why is this an important event?

## PSE: PART II: CARDIOVASCULAR PATHOLOGY

### AIM

To understand and gain facility in interpreting the relationship between the pathological processes of atherogenesis, thrombosis, embolism and infarction on the one hand, and their capacity to generate complex patterns of disease on the other.

### CASE

A 64-year old retired executive, whilst pottering in his garden, developed central crushing chest pain that radiated down his left arm. He was rushed into hospital where an electrocardiogram showed evidence of an acute myocardial infarction. A few hours later, blood tests showed elevation in the serum levels of both Troponin-I and the MB isotype of creatine kinase (an intracellular protein and an intracellular enzyme respectively, normally present only in cardiac myocytes).

The two photographs (**P22.5** and **P22.6**) show the microscopic appearances of myocardium 24 hours and 8 days after an episode of this type (from different cases), but may not have been numbered in the right order.

Catalogue Number	Small Image	Image Map	Large Image
A_VA_IF_HT_64.jpg	<a href="#">P22.5</a>		<a href="#">P22.5</a>
A_VA_IF_HT_65.jpg	<a href="#">P22.6</a>		<a href="#">P22.6</a>

- Q1.** Work out, and justify as fully as possible, whether **P22.5** was taken earlier than **P22.6** or the other way round.
- Q2.** What changes in the myocardial cells can explain (i) the raised levels of Troponin-I and MB isotype of creatine kinase; (ii) the pain?
- Q3.** What might you have found in a microscope section of the coronary artery, which supplied the infarcted wall of the left ventricle?

Five days after the initial admission to hospital, he was found unconscious on the floor. When he regained consciousness, he was no longer able to move his arm or leg on his right side. His face was also paralysed on this side.

Two days later, he developed severe abdominal pain and bloody diarrhoea. It was decided not to undertake surgery, given his condition. Instead, he was nursed and sedated. He died 2 days later and a post-mortem was performed.

### **P22.7 The patient's large and small intestines are shown at post mortem.**

Catalogue Number	Small Image	Image Map	Large Image
A_VA_IF_IT_01.jpg	<a href="#">P22.7</a>		<a href="#">P22.7</a>

- Q4.** What changes to the intestines can you see? How has this occurred? Why would this cause death?

### **P22.8 A post mortem section of brain** is also shown.

Catalogue Number	Small Image	Image Map	Large Image
A_VA_IF_BR_05.jpg	<a href="#">P22.8</a>		<a href="#">P22.8</a>

- Q5.** What has occurred to the brain and why did it occur?

**P22.9 & 10 Post mortem photograph of kidney & photomicrograph of post mortem kidney.**

Catalogue Number	Small Image	Image Map	Large Image
A_VA_IF_KD_10.jpg	<a href="#">P22.9</a>		<a href="#">P22.9</a>
A_VA_IF_KD_11.jpg	<a href="#">P22.10</a>		<a href="#">P22.10</a>

- Q6.** An abnormality was found in his kidney at post mortem. What shape is it? What does this suggest it is? Correlate the naked eye changes with the histological appearances.
- Q7.** Can you draw a flow diagram summarising the sequence of events from the pathological processes that triggered the myocardial infarction, to changes affecting brain, kidney & intestines, eventually leading to death?

**Please remember to collect an answer sheet at the end of the Problem Solving Exercise.**