Atherosclerosis Appendix

Atherosclerosis (ath-er-o-skle-RO-sis) is the hardening and narrowing of the arteries. It is a slow, progressive disease that starts in childhood. It is caused by the slow buildup of plaque (plak) on the inside of walls of the arteries. Arteries are blood vessels that carry oxygen-rich blood away from the heart to other parts of the body. (Note: the pulmonary arteries carry oxygen-poor blood away from the heart to the lungs).

Plaque is made up of fat, cholesterol, calcium, and other substances found in blood. The presence of oxidized LDL (low density lipoprotein) activates scavenger white blood cells, called macrophages. The macrophages begin to ingest as much of the oxidized LDL as possible and change into foam cells as a result. The newly formed foam cells begin releasing signals that initiate an immune response in the body. The buildup of plaque inside the walls of an artery narrows the inside diameter of that artery and, in time, may restrict blood flow. Plaque can be hard and stable or soft and unstable.

Hard plaque causes artery walls to thicken and harden. Soft plaque is more likely to break apart from the walls and expose the blood to abnormal tissue. This contact causes a thrombus (blood clot) that can partially or totally block the flow of blood in the artery. When this happens, the organ supplied by the blocked artery starves for blood and oxygen. The organ’s cells may either die or suffer severe damage.

Atherosclerosis can affect the arteries of the brain, heart, kidneys, arms, or legs. As plaque builds up, it can cause serious diseases and complications. These include:

- Coronary artery disease
  - Angina pectoris
  - Heart attack
  - Sudden death
- Cerebrovascular disease
  - Transient ischemic attack (TIA) or “mini strokes
  - Stroke
- Peripheral arterial disease

Retrieved and modified from the National Heart Lung and Blood website on April 14, 2005
Cross sectional views show three layers of a typical artery; see Figure 1, Layers of a Typical Artery.

1. **Intima** – inner layer of endothelial cells embedded in extracellular matrix
2. **Media** – separated from intima by elastic lamina & has smooth muscle cells, elastic laminae, bundles of collagen fibers and elastic fibrils all embedded in extracellular matrix
3. **Adventitia** – outer most variable layer with dense fibroelastic connective tissue, nutrient vessels and nerves

**Figure 1 Layers of a Typical Artery**
### “Cast of Characters” in the Images

<table>
<thead>
<tr>
<th>IMAGE</th>
<th>NAME</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Red Blood Cell (Erythrocyte)" /></td>
<td>Red Blood Cell (Erythrocyte)</td>
<td>Hemoglobin-containing cells that carry oxygen to body tissues and are responsible for the red color of vertebrate blood.</td>
</tr>
<tr>
<td><img src="image" alt="White Blood Cell (Leukocyte) Macrophage" /></td>
<td>White Blood Cell (Leukocyte) Macrophage  Left – no ingested lipoproteins  Right – with ingested lipoproteins</td>
<td>Phagocytic tissue cell that may be fixed or freely motile and functions to protect the body against infection and foreign substances.</td>
</tr>
<tr>
<td><img src="image" alt="White Blood Cell (Leukocyte)" /></td>
<td>White Blood Cell (Leukocyte)</td>
<td>Macrophage infiltrating through the blood vessel wall.</td>
</tr>
<tr>
<td><img src="image" alt="Foam cell" /></td>
<td>Foam cell</td>
<td>Macrophage cell filled with lipid inclusions which is typical of abnormal lipid metabolism.</td>
</tr>
<tr>
<td><img src="image" alt="White Blood Cell (Leukocyte)" /></td>
<td>White Blood Cell (Leukocyte)</td>
<td>A T-cell is a type of white blood cell that becomes specialized in the thymus, has highly specific antigen receptors on its cell membrane, and helps control immunity. Also called T lymphocyte.</td>
</tr>
<tr>
<td>Image</td>
<td>Name</td>
<td>Description</td>
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<tr>
<td><img src="image1" alt="Platelets" /></td>
<td><strong>Platelets</strong>&lt;br&gt;The platelet at the far left is inactivated and the images to the right show the changes in the platelets as they become activated.</td>
<td>Platelets are tiny, colorless, disk-like fragments derived from megakaryocyte cytoplasm. They lack a nucleus and are released from the bone marrow into the blood. Platelets help blood clot by adhering to other platelets and to damaged epithelium. Platelets are also called <em>thrombocytes</em>.</td>
</tr>
<tr>
<td><img src="image2" alt="Lipoprotein particle" /></td>
<td><strong>Lipoprotein particle</strong>&lt;br&gt;A complex of protein and lipid including HDL, LDL, and VLDL&lt;br&gt;<em>Note:</em> HDL = High Density Lipoprotein&lt;br&gt;LDL = Low Density Lipoprotein&lt;br&gt;VLDL = Very Low Density Lipoprotein</td>
<td>Smooth muscle is under involuntary nervous control. It allows hollow organs, such as blood vessels to contract.</td>
</tr>
<tr>
<td><img src="image3" alt="Smooth muscle cell" /></td>
<td><strong>Smooth muscle cell</strong>&lt;br&gt;Smooth muscle is under involuntary nervous control. It allows hollow organs, such as blood vessels to contract.</td>
<td>Endothelial cells are cells that group together to form a thin lining in the heart, blood vessels, lymph vessels, and hollow cavities of the body.</td>
</tr>
<tr>
<td><img src="image4" alt="Activated Endothelial cell" /></td>
<td><strong>Activated Endothelial cell</strong>&lt;br&gt;Endothelial cells are activated through protein signaling in response to foreign material. Activation allows some white blood cells leave the blood and migrate into inflamed tissues.</td>
<td></td>
</tr>
<tr>
<td><img src="image5" alt="White Blood Cell" /></td>
<td><strong>White Blood Cell</strong>&lt;br&gt;(Leukocyte) Neutrophil&lt;br&gt;Neutrophils are a type of white blood cell that help body cells destroy foreign matter they have ingested. Neutrophils are attracted by proteins from activated endothelium and macrophages.</td>
<td></td>
</tr>
</tbody>
</table>
**ANNOTATED ATHEROSCLEROSIS IMAGES**

This table is designed for teacher information; it indicates the correct sequence of the images and includes brief annotations about the processes occurring in each image.

<table>
<thead>
<tr>
<th>Image</th>
<th>Annotation</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image 1" /></td>
<td>The “Transparent Man” allows students to peek inside for a quick anatomical point of reference. The major blood vessels are included for illustration purposes and are not anatomically complete.</td>
</tr>
<tr>
<td><img src="image2.png" alt="Image 2" /></td>
<td>Zooming in for a closer look, this image helps students maintain a frame of reference as they progress to the coronary arteries for their exploration of atherosclerosis progression.</td>
</tr>
<tr>
<td><img src="image3.png" alt="Image 3" /></td>
<td>Closer to the disease site, the coronary arteries, which supply blood to the heart muscle, come into view. Atherosclerosis begins in the coronary arteries during youth and results in coronary artery disease in adults.</td>
</tr>
</tbody>
</table>
Looming larger, the left coronary artery is the most common area for atherosclerosis to develop. Atherosclerotic plaques do not develop in random locations; forces associated with blood flow interact with activated endothelium to determine where the plaques form.

Closing in on the left coronary artery, the blood vessel can be seen embedded in a layer of fat on the surface of the heart muscle. Notice the background color of fat can be seen in subsequent images.

The left coronary artery is shown with a “cut away” area marked. This area of the vessel wall will lift off in future frames to allow a peek inside.
The “cut away” area lifts, showing the artistic rendering of a typical blood vessel. **Red blood cells, white blood cells, and platelets** can be seen floating in the plasma of the blood. The yellow droplets represent **lipoprotein particles** in the blood plasma and beneath the intima. **Lipoprotein particles** are the principal way in which lipids, such as cholesterol, are carried through the blood and they can infiltrate the blood vessel wall. The number of **lipoprotein particles** present in blood is a predictor of cardiovascular disease. Notice also the blue **endothelial cells** of the intima lining the inside of the blood vessel. The **media** and **adventitia** can also be seen as well.

**Low Density Lipoprotein (LDL)** particles are oxidized as they move through the endothelial cells into the intima. **LDL** cholesterol is sometimes called “bad” cholesterol because high **LDL** levels in the blood lead to a buildup of cholesterol in artery walls. Special receptors on **macrophages** (scavenger white blood cells) allow them to respond to the presence of oxidized **LDL** as seen in the large macrophage approaching the collection of **LDL** particles in the intima.

**Macrophages** are scavenger cells that migrate into all tissues, including arterial walls. Specialized **receptors** allow macrophages to detect and ingest **oxidized LDL**, effectively isolating this foreign material. However, if **LDL** levels in the blood remain high, more and more lipoprotein particles will accumulate in the arterial wall, overwhelming the ability of macrophages to ingest them.
Macrophages that have ingested oxidized LDL become foam cells. Once the transformation has occurred, the foam cells have a different appearance under the microscope. Foam cells produce factors that activate the endothelium (observe the shading on activated endothelial cells). Activated endothelium leads to increased permeability, leukocyte adhesion to the endothelium, and leukocyte migration. As the process accelerates and foam cells collect under the endothelium, a fatty streak is created.

Elevated LDL in the blood causes recruitment of macrophages and the continued uptake of oxidized LDL. The accumulation of foam cells causes a visible fatty streak in the artery. Fatty streaks occur in the aortas and coronary arteries of almost all young people by the age of twenty and seem to be a “condition of living” rather than a disease state. Foam cells release factors (cytokines) that further accelerate the inflammatory response in surrounding tissues. The progression of atherosclerosis is an active process and at this point can be successfully reversed with favorable lifestyle changes.

Structural changes (vascular remodeling) in the blood vessel begin to occur; note the movement of smooth muscle cells. The number of foam cells increases and this increase will accelerate the inflammatory process.
The disruption of arterial structure is more pronounced. **Degradation of the foam cells** causes the ingested lipid to be released into the **plaque** that is forming in the arterial wall. Note the **T-lymphocytes** (green) have infiltrated the intima. **T-lymphocytes** will orchestrate the expanding immune response.

The developing plaque forms a **fibrous cap**, more **lipid material accumulates** from degrading foam cells, and the **number of T-lymphocytes increases** as the disease process progresses.

**Rupture of the plaque** begins, **fibrin** is formed and **platelets are activated**. Notice the irregular shape of the activated platelets in the lumen of the blood vessel. Red blood cells will become trapped in the fibrin network, ultimately creating a well-defined **thrombus**.
The clotting process escalates in this image, increasing the risk that this thrombus may obstruct the blood flow that supplies the heart muscle. There is also the chance that the thrombus may break loose and obstruct the blood supply at another location in the coronary artery. If either of these events occurs, the heart muscle may be seriously damaged from lack of food and oxygen.

The size of the thrombus increases, and if it completely blocks the artery, it is likely to cause a heart attack.

The view changes to an external view of the heart.
<table>
<thead>
<tr>
<th>The transparent man grabs his chest in pain.</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Image of a transparent man with heart highlighted]</td>
</tr>
<tr>
<td>The heart attack is in progress!</td>
</tr>
<tr>
<td>![Image of a man with red area indicating heart attack]</td>
</tr>
</tbody>
</table>
Adventitia - The outer layer that makes up a tubular organ or structure and especially a blood vessel, is composed of collagenous and elastic fibers, and is not covered with peritoneum — called also tunica adventitia or tunica externa.

Cholesterol - A steroid alcohol C_{27}H_{45}OH present in animal cells and body fluids that regulates membrane fluidity, functions as a precursor molecule in various metabolic pathways, and as a constituent of LDL may cause arteriosclerosis.

Coronary Artery - Either of two arteries that arise one from the left and one from the right side of the aorta immediately above the semilunar valves and supply the tissues of the heart itself.

Coronary Artery Disease - A condition (as sclerosis or thrombosis) that reduces the blood flow through the coronary arteries to the heart muscle — called also coronary disease or coronary heart disease.

Endothelium - An epithelium of mesoblastic origin composed of a single layer of thin flattened cells that lines internal body cavities (as the serous cavities or the interior of the heart).

Fatty Streak - A small, flat, yellow-gray area, composed mainly of cholesterol-laden macrophages, within an artery; possibly an early stage of atherosclerosis.

Fibrin - White insoluble fibrous protein formed from fibrinogen by the action of thrombin especially in the clotting of blood.

Fibrinogen - A plasma protein that is produced in the liver and is converted into fibrin during blood clot formation.

Fibrous cap - The fibrous cap is a layer of fibrous connective tissue, which is thicker and less cellular than the normal intima. The fibrous cap contains macrophages and smooth muscle cells, among other substances.

Foam Cells - Scavenger white blood cells (Macrophages) which have ingested oxidized lipoproteins - they release factors which initiate an immune response in the body.

Heart attack - An acute episode of heart disease (as myocardial infarction) due to insufficient blood supply to the heart muscle itself especially when caused by a coronary thrombosis or a coronary occlusion.

Intima - the innermost coat of an organ (as a blood vessel) consisting usually of an endothelial layer backed by connective tissue and elastic tissue — called also tunica intima.

Lipoprotein Particles - These are made of lipids and various proteins. Lipoprotein particles transport lipids, such as cholesterol, through the blood. These are the particles that can build up in a person’s arteries and cause heart attacks. There are three major types of lipoprotein particles:

- Low Density Lipoproteins (LDL)
- High Density Lipoproteins (HDL)
- Very Low Density Lipoproteins (VLDL)
Determining one’s risk for heart disease is not just based upon cholesterol level. No matter how much cholesterol is being carried by these lipoprotein particles, it is the number of lipoprotein particles in the blood that contribute to heart disease.

**Macrophages** - A phagocytic tissue cell of the mononuclear phagocyte system that may be fixed or freely motile and is derived from a monocyte, and functions in the protection of the body against infection and noxious substances.

**Media** - The middle coat of the wall of a blood or lymph vessel consisting chiefly of circular muscle fibers — called also tunica media.

**Oxidized**

1. to combine with oxygen
2. to dehydrogenate especially by the action of oxygen
3. to change (a compound) by increasing the proportion of the electronegative part or change (an element or ion) from a lower to a higher positive valence; to remove one or more electrons from an atom, ion, or molecule

**Plaque** - This is an atherosclerotic lesion.

**Plasma** - The fluid part especially of blood, lymph, or milk that is distinguished from suspended material.

**Platelets** - A minute colorless anucleated disk-like body of mammalian blood that is derived from fragments of megakaryocyte cytoplasm, that is released from the bone marrow into the blood, and that assists in blood clotting by adhering to other platelets and to damaged epithelium — also called blood platelet, thrombocyte.

**Red Blood Cell (Erythrocyte)** - Any of the hemoglobin-containing cells that carry oxygen to the tissues and are responsible for the red color of vertebrate blood — also called erythrocyte, red blood corpuscle, red cell, red corpuscle.

**Thrombus** - A clot of blood formed within a blood vessel and remaining attached to its place of origin.

**T-lymphocyte** - Any of several lymphocytes (as a helper T cell) that differentiate in the thymus, possess highly specific cell-surface antigen receptors, and include some that control the initiation or suppression of cell-mediated and humoral immunity (as by the regulation of T and B cell maturation and proliferation) and others that lyse antigen-bearing cells — also called T lymphocyte.

**Vascular remodeling** - The persistent change to the structure of the arterial wall.

**White Blood Cell** - Any of the blood cells that are colorless, lack hemoglobin, contain a nucleus, and include the lymphocytes, monocytes, neutrophils, eosinophils, and basophils — also called leukocyte, white blood corpuscle, white cell, white corpuscle.

These definitions were retrieved and modified from Dorland’s Medical Dictionary and Medline Plus on April 25, 2005.
Websites Used:

Dorland’s Medical Dictionary WB Saunders Harcourt Health Services
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http://www.merckmedicus.com

Medline Plus
U.S. National Library of Medicine, 8600 Rockville Pike, Bethesda, MD 20894

National Heart Lung and Blood website on April 14, 2005
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