Cholesterol accumulation in atherosclerotic plaque has long been assumed to occur mainly in monocyte-derived macrophages. Using a combination of enhanced lipid fixation and cell-specific immunohistochemical techniques as well as fluorescence-activated cell sorting we have determined that smooth muscle cells comprise at least 50% of the foam cell population in human coronary artery atherosclerosis. We have also found that 35-40% of cells expressing classic macrophage markers in human atherosclerosis are of smooth muscle cell rather than myeloid-lineage origin. The mechanism of accumulation of excess cholesterol in smooth muscle cells may be the specific loss of expression of the cholesterol transporter ATP-binding cassette transporter A1 (ABCA1) in these cells but not myeloid-lineage cells. These results affect the way we think of the pathogenesis of and cholesterol metabolism in atherosclerotic lesions, and suggest novel therapeutic strategies are needed to reduce cholesterol accumulation in the artery wall and the resulting ischemic vascular events.