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Atherosclerosis: The Apolipoprotein E-Deficient Mouse Model Revisited

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The apolipoprotein E-deficient mouse model is an excellent experimental model for studying hypercholesterolemia and the spontaneous development of atherosclerosis. The pathogenesis of the atherosclerotic lesion development mimics that found in humans and is especially prominent in the aortic arch. We have followed the development of atherosclerotic lesions in the aortic arch of apolipoprotein E knockout mice aged 6 weeks to 18 months in 1μm epoxy-resin sections stained with alkaline toluidine blue. The lesion progression involves:

(1) Initiation. Endothelial cells lining the lumen in the earliest stages of atherosclerosis are very bunched with pronounced, rounded nuclei projecting into the lumen. The outer lining of the subendothelial space becomes very crenated.

(2) Subendothelial space. The subendothelial space enlarges with the apparent accumulation of fluid followed by invasion by isolated macrophages containing many small cytoplasmic lipid droplets (Fig.1).

(3) Fatty-streak formation. The macrophages in the subendothelium become closely packed and accumulate in large groups and undergo severe necrotic changes. The remains of the necrotic macrophages amalgamate to form large pools of lipid-rich material, which develops throughout the subendothelium and developing plaque. At this time aggregates of needle-like cholesterol (cholesterol clefts) become prominent in the subendothelium and increase in number (Fig.2).

(4) Changes in the *Tunica media*. The elastic membranes of the *Tunica media* become discontinuous at the sites of the developing plaque. This occurs at first in the most internal membranes, but eventually this continues (in parallel) throughout all the elastic membranes in specific regions (right through to the *Adventitia*). Macrophages invade the *Tunica media*. The smooth muscle cells of the *Tunica media* begin to accumulate lipid droplets. The muscle cells proliferate and the myocytes change from a concentric circular configuration to a more radial format. The nuclei of these smooth muscle cells multiply and individual myocytes often show adjacent chains of 5 or more contiguous nuclei.

(5) Calcification. The cells of the media in more advanced lesions become rounded and begin secreting a new intercellular matrix (stained blue in toluidine blue-stained epon sections). The matrix becomes calcified (seen as white deposits). By this stage the aortic wall is hardened and inflexible (arteriosclerotic).

(6) Occlusion of the lumen. In advanced atherosclerotic lesions the plaque develops in a dome-like manner leading to progressive occlusion of the lumen. In apolipoprotein E-deficient mice aged 17-18 months, the occlusion can be over 90%.

(7) Unstable plaque. In many stages of plaque development finger-like protrusions of the subendothelial space covered by a very thin (squamous) endothelial layer with accumulations of macrophages extend into the lumen. In many cases the macrophages of the protrusions appear to escape into the lumen.

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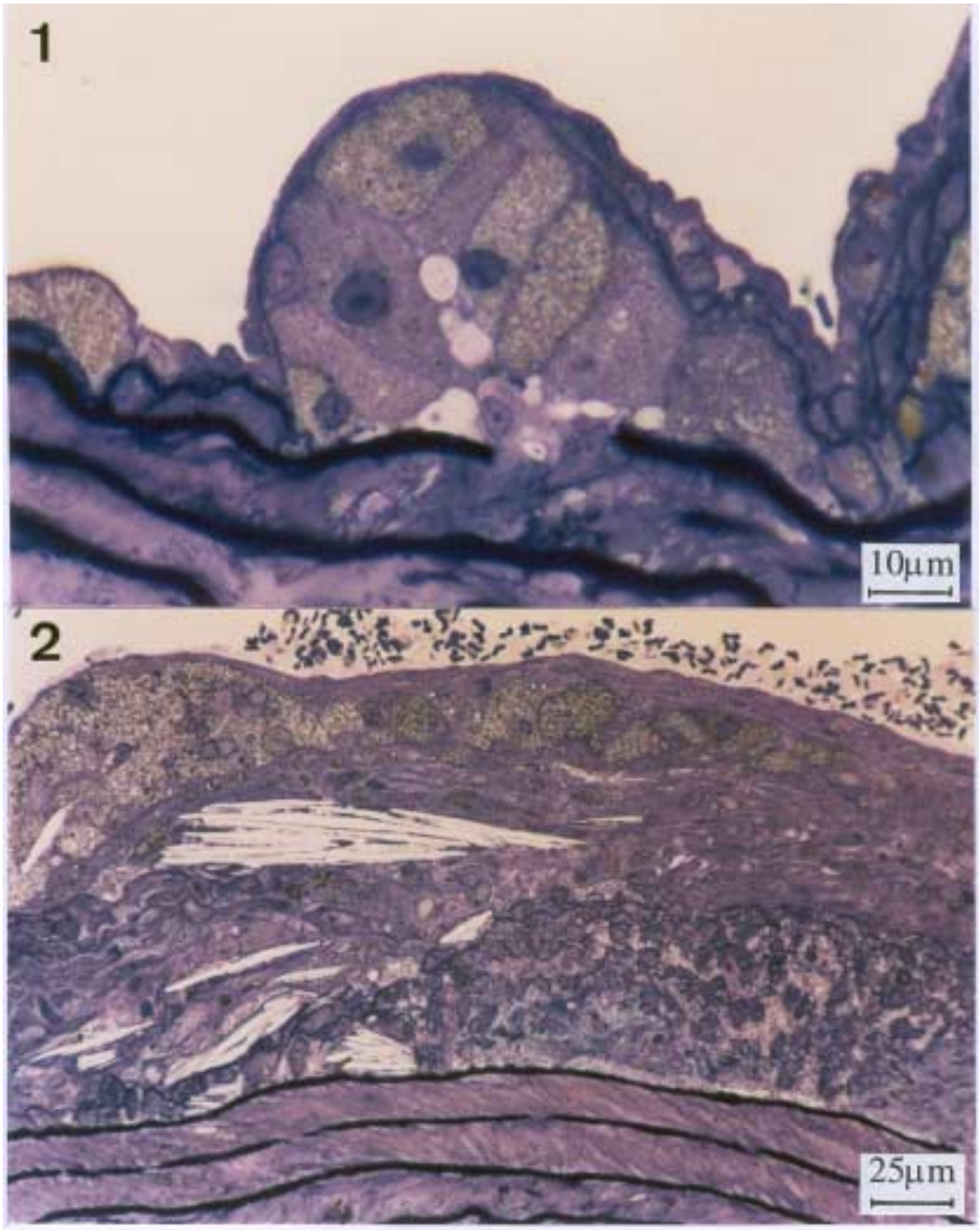

Fig.1. Early "fatty streak" (4 month old mouse). Lipid-filled macrophages accumulate in the subendothelial space. Note also disruptions in elastic membranes of T. media.
Fig.2. More advanced and complex lesion (8 month old mouse). The elongated white needle-like bodies are cholesterol deposits.

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