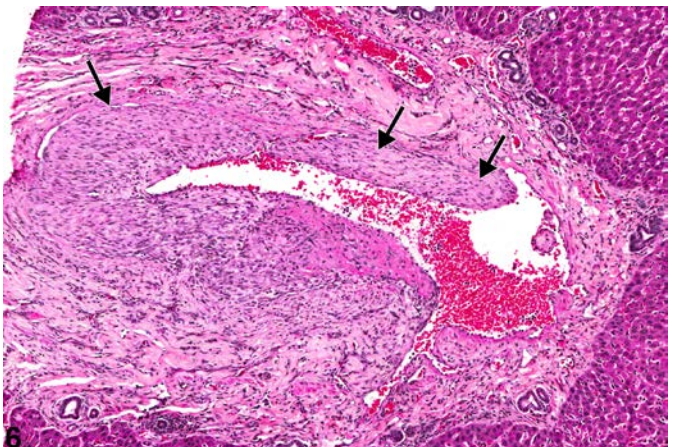
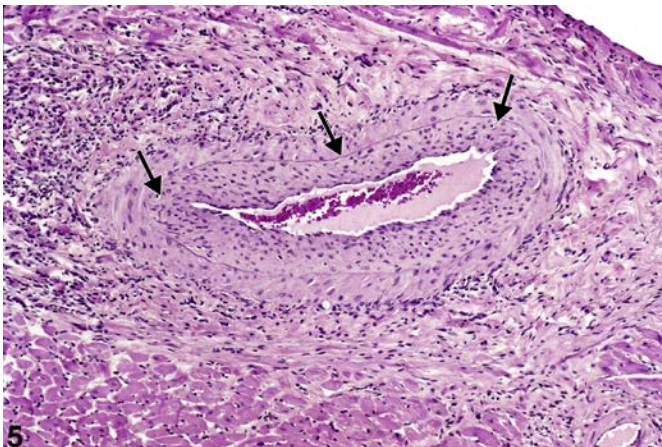
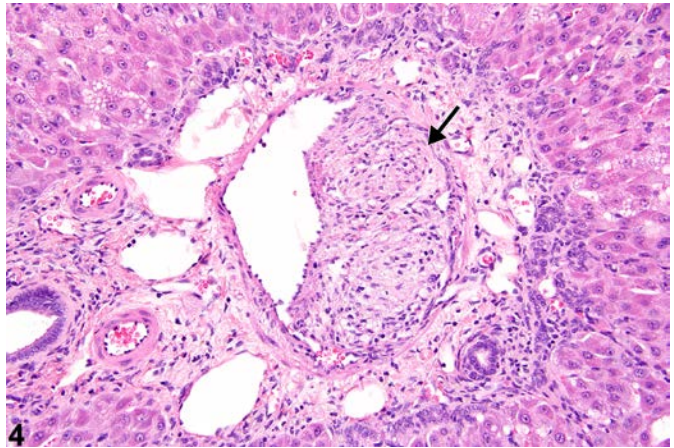
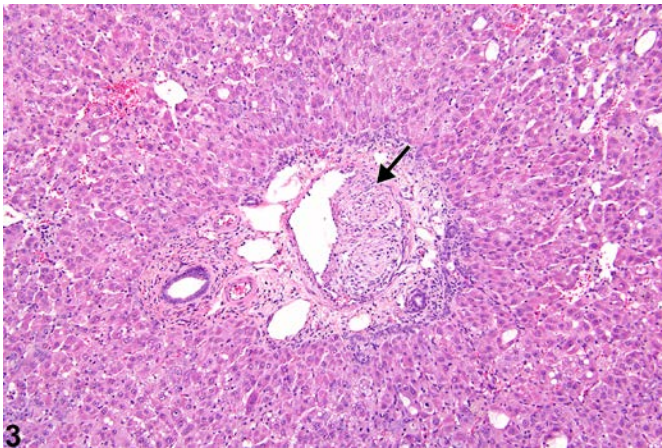
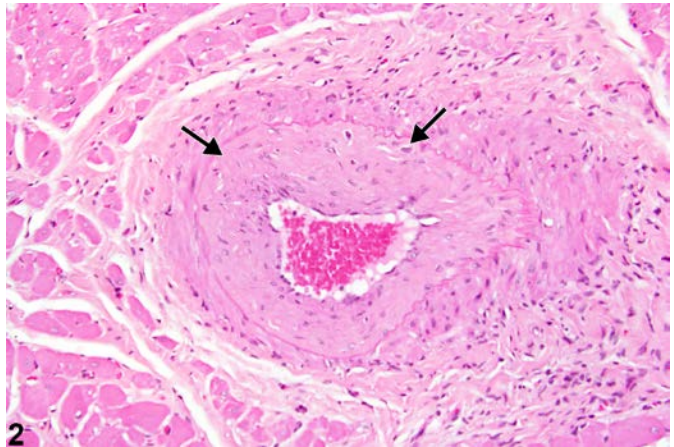
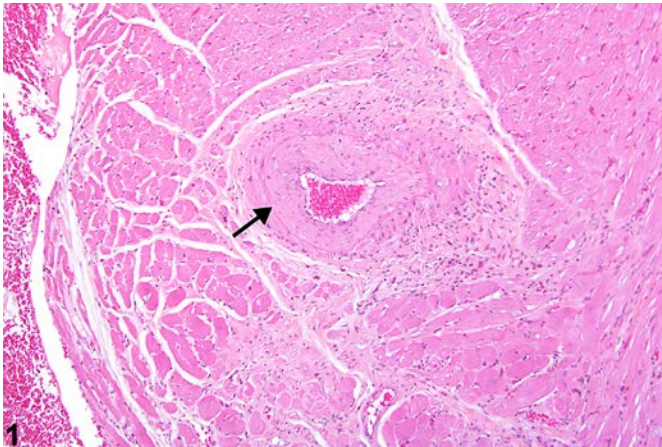
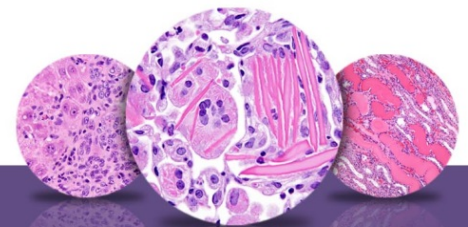


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Blood Vessel – Proliferation, Intimal





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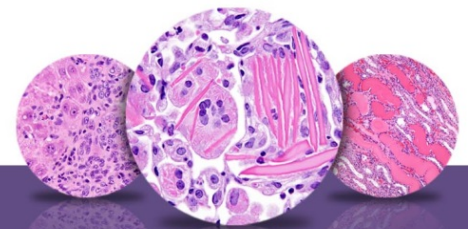
Blood Vessel – Proliferation, Intimal

Figure Legend: **Figure 1** Heart, Artery - Proliferation, Intimal in a male F344/N rat from a chronic study. The wall of an artery in the heart is thickened (arrow). **Figure 2** Heart, Artery - Proliferation, Intimal in a male F344/N rat from a chronic study (higher magnification of Figure 1). There is a distinct demarcation between the thickened tunica intima and the tunica media (arrows). **Figure 3** Liver, Artery - Proliferation, Intimal in a female F344/N rat from a subchronic study. There is segmental thickening of a large artery (arrow). **Figure 4** Liver, Artery - Proliferation, Intimal proliferation in a female F344/N rat from a subchronic study (higher magnification of Figure 3). The intimal proliferation (arrow) is causing partial occlusion of the arterial lumen. **Figure 5** Heart, Artery - Proliferation, Intimal in a male F344/N rat from a chronic study. The junction between tunica media and the tunica intima (arrows) is distinct. **Figure 6** Liver, Artery - Proliferation, Intimal in a male F344/N rat from a chronic study. The line of demarcation between the proliferating tunica intima and the tunica media (arrows) is conspicuous.

Comment: Intimal proliferation (Figure 1, Figure 2, Figure 3, Figure 4, Figure 5, and Figure 6) is characterized by thickening of the tunica intima of blood vessels, with the normal single-layered intima, beneath the endothelium, expanded into a multilayered cellular lining. The increased thickness of the intima results from a combination of endothelial hypertrophy, proliferation of smooth muscle cells, and accumulation of glycosaminoglycans. (For comparison, see the photo of normal blood vessel in the introductory comments.)

Endothelial injury releases inflammatory mediators that recruit leukocytes to the area. These cells express growth factors that promote smooth muscle cell migration from the tunica media into the intima. In other cases, pluripotent stem cells migrate from the basement membrane in response to injury. These cells proliferate in the tunica intima and deposit extracellular matrix, leading to thickening of the intima and a reduction in the vascular lumen. Intimal proliferation is an important cause of restenosis, a common complication of endovascular intervention in humans and animal models of vascular disease.

Strains differ in susceptibility to intimal proliferation. C57BL/6, 129SV, SJL/J, C3H, and iNOS-knockout mice are more resistant to the development of intimal proliferation after vascular injury, while FVB/N, C57L/J, and apoE-, RAG2-, eNOS-, and LDLR-knockout mice are highly susceptible to intimal proliferation following vascular injury. Intimal proliferation may also be induced through mechanical injury to the endothelium. The most commonly used procedures to induce arterial injury in mice are



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carotid artery ligation with cessation of blood flow, and mechanically induced denudation of endothelium in the carotid or femoral arteries. Both procedures result in intimal proliferation after two to three weeks.

Recommendation: Whenever present, intimal proliferation of blood vessels should be diagnosed and graded. The organ(s) in which it occurs should be included in the diagnosis as the site, and the type of blood vessel affected (e.g., artery or vein) should be included as a site modifier. If the type of blood vessel cannot be determined, the site modifier “blood vessel” may be used. Lesions in protocol-required great vessels, such as aorta, should be recorded with the blood vessel as the site (e.g., Aorta – Proliferation, Intimal). The severity grade should be based on the extent of the lesion (e.g., number of arteries affected, length of vessel affected) and severity of the lesion (e.g., degree of thickening, percentage of luminal occlusion).

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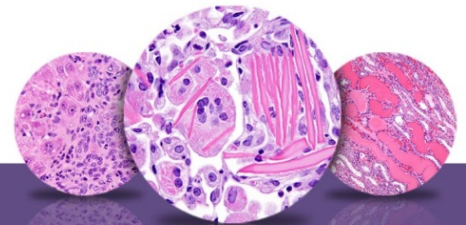
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