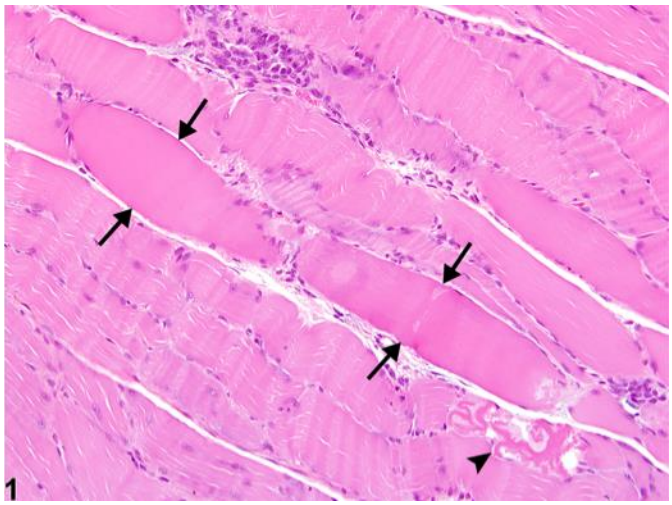
Skeletal Muscle – Degeneration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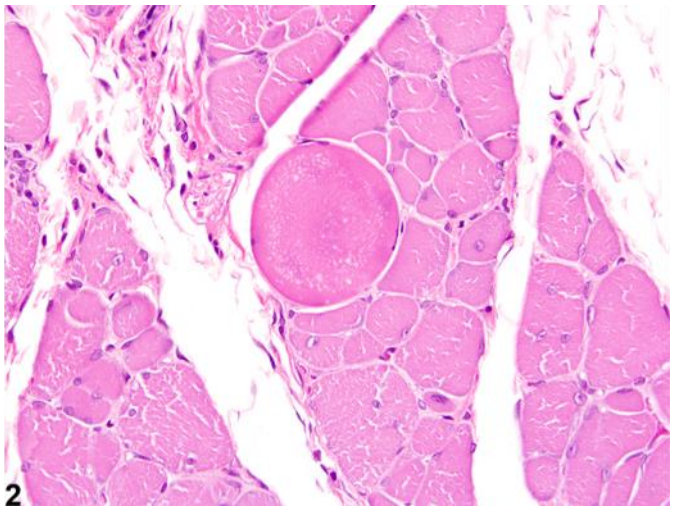
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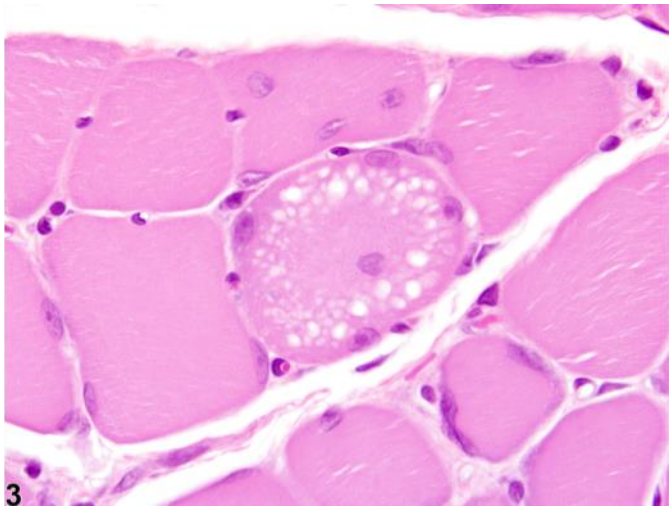
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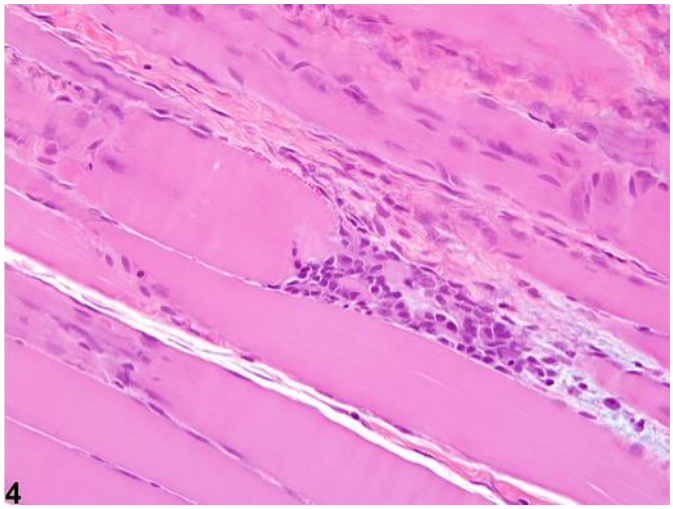
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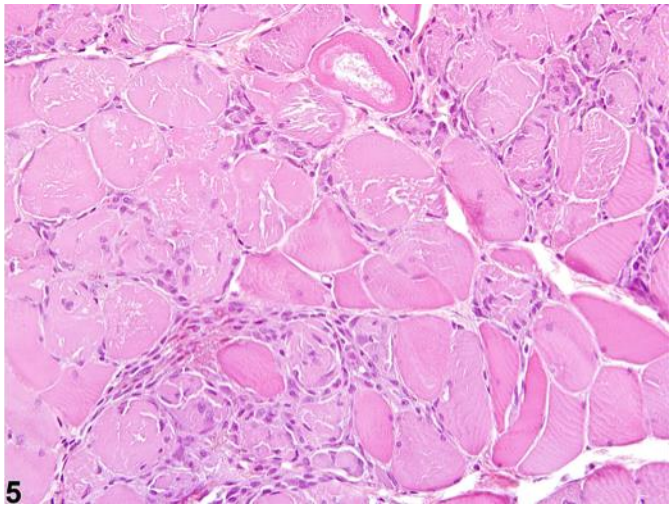
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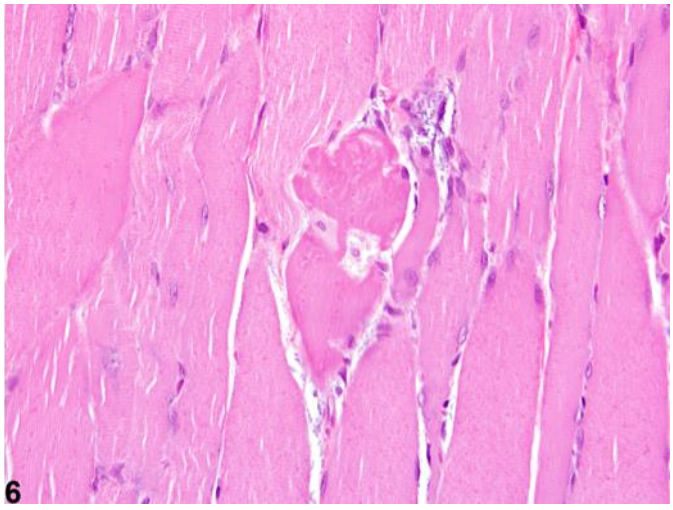
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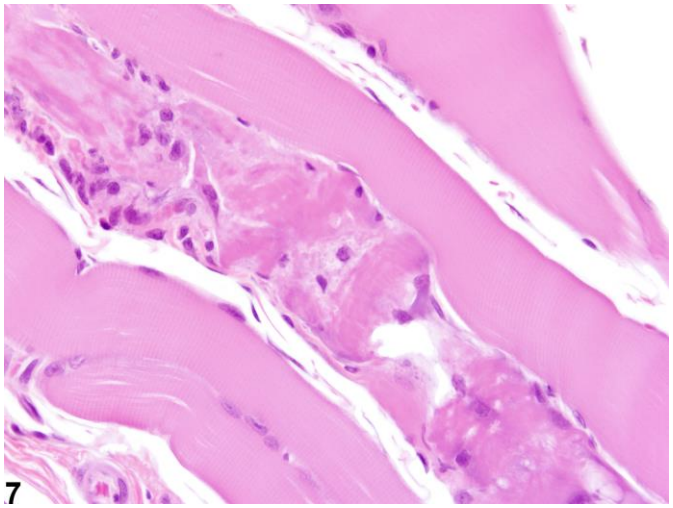

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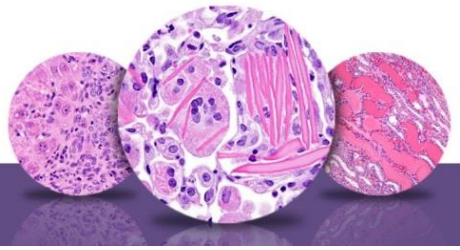
Figure Legend: **Figure 1** Skeletal muscle - Degeneration in a male Harlan Sprague-Dawley rat from a subchronic study. A central myofiber is swollen and hypereosinophilic (arrows), and a fragmented segment of another fiber (arrowhead) demonstrates segmental degeneration. **Figure 2** Skeletal muscle - Degeneration in a male Harlan Sprague-Dawley rat from a subchronic study. An enlarged, hypereosinophilic muscle fiber with subtle vacuolation is present in an otherwise normal muscle bundle. **Figure 3** Skeletal muscle - Degeneration in a male Harlan Sprague-Dawley rat from a subchronic study. A rounded fiber contains multiple peripheral nuclei, a single internal nucleus, and abundant cytoplasmic vacuoles. **Figure 4** Skeletal muscle - Degeneration in a male Harlan Sprague-Dawley rat from a subchronic study. Multiple macrophages and interstitial cells have phagocytized degenerative portions of an enlarged muscle fiber. **Figure 5** Skeletal muscle - Degeneration in a male F344/N rat from a chronic study. In this cross section of muscle, several adjacent muscle fibers exhibit multiple features of degeneration; increased sarcolemmal nuclei are indicative of an early regenerative response. **Figure 6** Skeletal muscle - Degeneration in a male Harlan Sprague-Dawley rat from a subchronic study. Degeneration is represented by a swollen, hyalinized, and partly fragmented muscle fiber. **Figure 7** Skeletal muscle - Degeneration in a male Harlan Sprague-Dawley rat from a subchronic study. A fragmented and partly hyalinized muscle fiber has lost its striations and is accompanied by early infiltration of macrophages.

Comment: Degenerated muscle can grossly appear either pale or dark. Histologically, degenerating myofibers can exhibit a variety of microscopic changes, including cell swelling, hypereosinophilia,



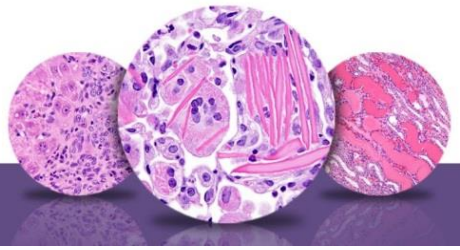
Skeletal Muscle – Degeneration

vacuolation, loss of striation, fragmentation, and rupture of fibers (Figure 1, Figure 2, Figure 3, Figure 4, Figure 5, Figure 6, and Figure 7). Ruptured fibers can often be identified by the presence of “retraction caps,” which are concavities at the free ends of the ruptured fibers. Macrophages are often noted in close association with degenerating myofibers, as they play an important role in phagocytizing associated debris (Figure 4). Due to the long length of muscle fibers, degeneration often only affects a segment or several segments of the fiber, as opposed to the entire myofiber. Regions of degeneration can be variably accompanied by additional myopathic changes, such as necrosis, atrophy, compensatory hypertrophy, regeneration, and fibrosis (Figure 5).

Degeneration is a common sequela of myofiber injury, regardless of the cause. Common causes include chemical irritants/myotoxins, abnormal metabolism, trauma, and infection. As in other tissues, degeneration can be reversible; however, if the injurious stimulus persists, a "point of no return” will be reached. When this occurs, the degenerative process becomes irreversible and myofiber necrosis follows.

Degeneration and necrosis represent a continuum of lesions and therefore are often both present within a given lesion. Due to the limited repertoire of skeletal muscle responses, they share similar morphologic features and can thus be difficult to differentiate histologically. This can create a diagnostic challenge. When evaluating a toxicity study, it is important for the pathologist to establish distinct criteria for both lesions and to be consistent and careful when applying them. Criteria should be described in the narrative. The term “myopathy” is commonly used to describe disorders of skeletal muscle in which degeneration and necrosis are key features. However, since myopathy is a general term and one that typically encompasses a collection of lesions rather than one distinct lesion, its use is not recommended.

Recommendation: When present, myofiber degeneration should be diagnosed and graded. If both degeneration and necrosis are present in a study, the predominant lesion should be diagnosed and the other described in the pathology narrative. However, the pathologist may record both lesions if it best describes the changes that are occurring. Concomitant regeneration should be recorded separately and assigned a severity grade when present to a significant extent. Other secondary lesions, such as



Skeletal Muscle – Degeneration

inflammation and hemorrhage, should not be diagnosed separately unless warranted by severity but should be described in the narrative.

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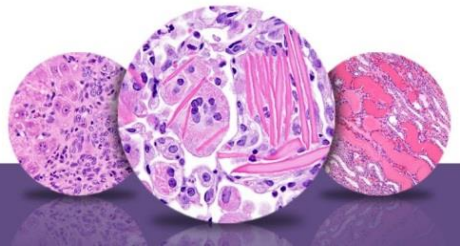

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Author:

Torrie A. Crabbs, DVM, DACVP
Pathologist
Experimental Pathology Laboratories, Inc.
Research Triangle Park, NC