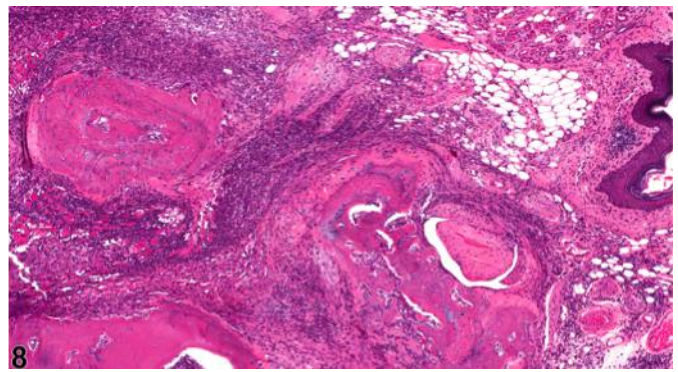
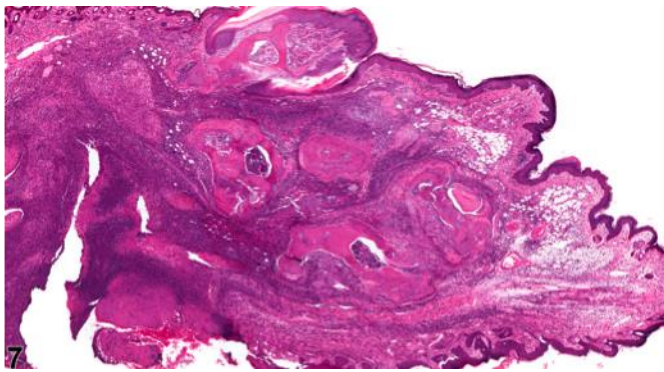
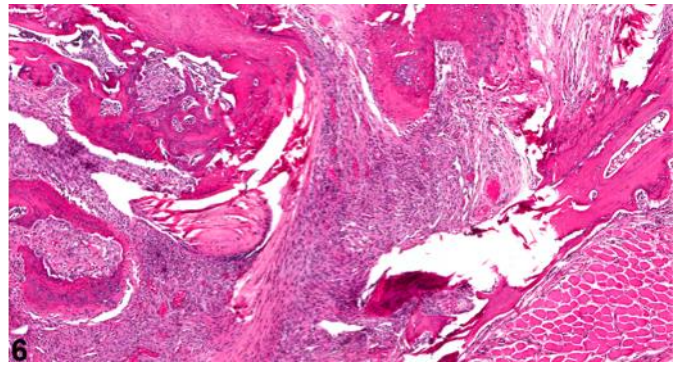
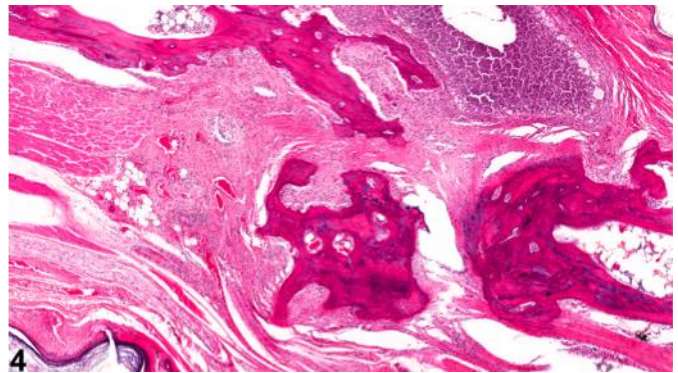
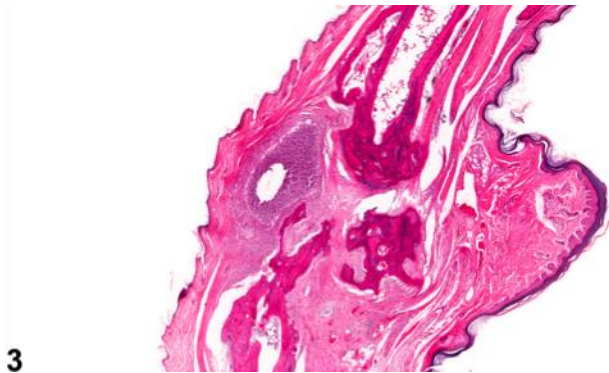
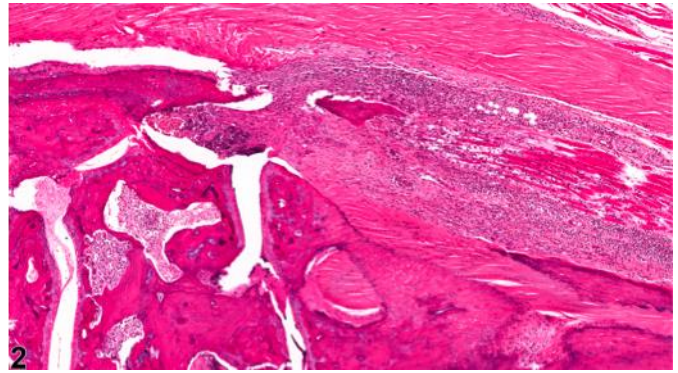
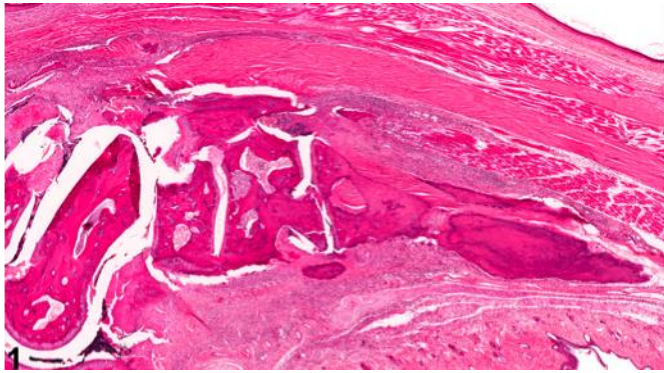
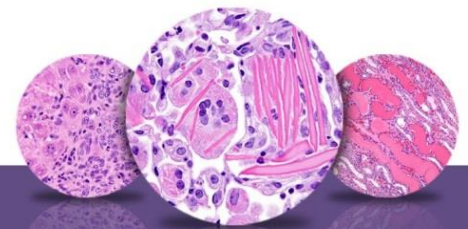


NTP Nonneoplastic Lesion Atlas

Bone, Joint – Inflammation



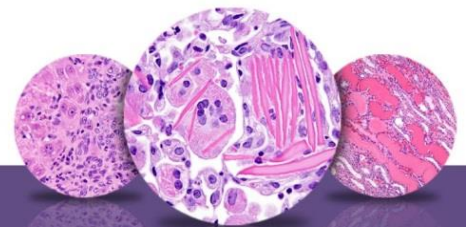


NTP Nonneoplastic Lesion Atlas

Bone, Joint – Inflammation

Figure Legend: **Figure 1** Bone, Joint - Inflammation, Chronic in a male B6C3F1/N mouse from a chronic study. There is a marked inflammatory infiltrate within the periarticular soft tissues and subjacent to the articular space and periosteal bone of the joint. **Figure 2** Bone, Joint - Inflammation, Chronic in a male B6C3F1/N mouse from a chronic study (higher magnification of Figure 1). There is a marked inflammatory infiltrate within the periarticular soft tissues and subjacent to the articular space and periosteal bone of the joint. **Figure 3** Bone, Joint - Inflammation, Chronic in a male B6C3F1/N mouse from a chronic study. This section of metatarsal joint shows inflammation in the periarticular tissues that extends into the subjacent joint space; marked fibroplasia and bony remodeling are also present. **Figure 4** Bone, Joint - Inflammation, Chronic in a male B6C3F1/N mouse from a chronic study (higher magnification of Figure 3). This section of metatarsal joint shows inflammation in the periarticular tissues that extends into the subjacent joint space; marked fibroplasia and bony remodeling are also present. **Figure 5** Bone, Joint - Inflammation, Chronic-active in a male B6C3F1/N mouse from a chronic study. There is severe inflammation within the tarsal joint space and surrounding tissues. **Figure 6** Bone, Joint - Inflammation, Chronic-active in a male B6C3F1/N mouse from a chronic study (higher magnification of Figure 5). This section of the tarsus shows severe inflammation within the joint space and surrounding tissues. **Figure 7** Bone, Joint - Inflammation, Suppurative in a female Swiss CD-1 mouse from a chronic study. There is marked suppurative inflammation, extensive fibroplasia, and bony remodeling in the paw and digits. **Figure 8** Bone, Joint - Inflammation, Suppurative in a female Swiss CD-1 mouse from a chronic study (higher magnification of Figure 7). This section of paw and digits shows marked suppurative inflammation, extensive fibroplasia, and bony remodeling.

Comment: Most incidences of inflammation of the joints (arthritis) (Figure 1, Figure 2, Figure 3, Figure 4, Figure 5, Figure 6, Figure 7, and Figure 8) involve the distal joints of the legs and feet (tarsus, carpus, metatarsus, metacarpus). They are characterized by infiltration of inflammatory cells; proteinaceous material and fibrin within the joint space and associated connective tissues; hyperplasia, edema, and fibrosis of the synovial membranes; and reactive new bone formation. Inflammation may induce thickened synovial membranes that cover the articular surfaces of the joint (pannus) or may undermine the articular cartilage by eroding subchondral bone. When chronic and severe, inflammation of the joint may lead to osteophytosis and ankylosis (fusion) of the joint. In contrast to osteoarthritis

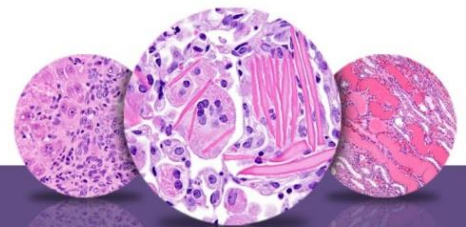


NTP Nonneoplastic Lesion Atlas

Bone, Joint – Inflammation

(degenerative joint disease; see “Bone, Joint - Degeneration”), arthritis due to microbial infection is associated with copious fluid and fibrinous exudate within the joint space. When a single joint is affected, a penetrating wound is the most likely cause, although microbial agents may also gain access to the joint via extension from adjacent tissues or through the bloodstream. Infectious causes of joint inflammation are uncommon in the B6C3F1 mouse and F344 rat. However, penetrating wounds, fighting, or other trauma may lead to localized microbial infections involving the joint or periarticular tissues. Test article exposures have not been associated with increased incidences of joint inflammation in NTP studies. It is possible that treatment with immunosuppressive compounds may affect an animal’s ability to combat small, localized infections, which may lead to joint inflammation when the joint space is involved, or result in systemic spread leading to multiorgan involvement, including polyarthritis. However, while pathogens associated with arthritis have been recognized in rodents in general, they are not typically observed as a cause of joint inflammation in routine toxicity and carcinogenicity studies.

In NTP studies, there are five standard categories of inflammation: acute, suppurative, chronic, chronic-active, and granulomatous. In *acute inflammation*, the predominant infiltrating cell is the neutrophil, though fewer macrophages and lymphocytes may also be present. There may also be evidence of edema or hyperemia. The neutrophil is also the predominant infiltrating cell type in *suppurative inflammation*, but the neutrophils are aggregated, and many of them are degenerate (suppurative exudate). Cell debris, both from the resident cell populations and from infiltrating leukocytes; proteinaceous fluid containing fibrin, fewer macrophages, occasional lymphocytes, and/or plasma cells; and possibly an infectious agent may also be present within the exudate. Grossly, these lesions would be characterized by the presence of pus. In the tissue surrounding the exudate, there may be fibroblasts, fibrous connective tissue, and mixed inflammatory cells, depending on the chronicity of the lesion. Chronic and chronic-active inflammation is determined by the presence of fibroblasts or fibrosis. With *chronic inflammation*, the predominant inflammatory cell is usually the lymphocyte, whereas in *chronic-active inflammation* it is a mixture of lymphocytes and neutrophils. Both lesions may also contain macrophages. However, it is the presence of fibroblasts or fibrosis that determines the chronic nature of the lesion. *Granulomatous inflammation* is another form of chronic inflammation, but this



NTP Nonneoplastic Lesion Atlas

Bone, Joint – Inflammation

diagnosis requires the presence of a significant number of aggregated, large, activated macrophages, epithelioid macrophages, or multinucleated giant cells.

Recommendation: When present, this lesion should be diagnosed and given a severity grade. In addition, the type of inflammation (acute, suppurative, chronic, chronic-active, or granulomatous) should be included in the diagnosis as a modifier. Any potential pathogenesises of the lesion should be discussed in the pathology narrative. If joint inflammation occurs as an extension of an inflammatory process from the periarticular soft tissues or overlying dermis (Figure 3 and Figure 4), it should not be diagnosed separately, but the extent of the lesion can be described in the narrative. The individual components of the lesion (e.g., synovial hyperplasia, hemorrhage, degeneration of cartilage, necrosis) should not be diagnosed separately unless warranted by severity but should be described in the narrative.

References:

Leininger JR, Riley MGI. 1990. Bones, joints, and synovia. In: Pathology of the Fischer Rat: Reference and Atlas (Boorman G, Eustis SL, Elwell MR, Montgomery CA, MacKenzie WF, eds). Academic Press, San Diego, 209-226.

Long PH, Leininger JR. 1999. Bones, joints, and synovia. In: Pathology of the Mouse (Maronpot R, Boorman G, Gaul BW, eds). Cache River Press, St Louis, 645-678.

Long PH, Leininger JR, Ernst H. 1996. Proliferative lesions of bone, cartilage, tooth, and synovium in rats, MST-2. In: Guides for Toxicologic Pathology. STP/ARP/AFIP, Washington, DC.

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