

# NON-PROLIFERATIVE LESIONS OF BONE, CARTILAGE, TOOTH, AND SYNOVIUM IN RATS

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## INTRODUCTION

The following are guidelines for standardizing terminology and diagnostic criteria for non-proliferative lesions of bone, cartilage, tooth, and synovium in rats. In addition, the rationale for selecting various terms and the use of commonly used synonyms are discussed. The term *non-proliferative* is used here to refer to non-neoplastic and non-preneoplastic alterations. The benefits of standardizing terminology and diagnostic criteria are improved consistency of toxicologic pathology data and improved communication among toxicologic pathologists.

## BONE

Non-proliferative bone lesions include non-neoplastic and non-preneoplastic bone alterations in which there is localized or generalized loss of bone mass (inflammation, necrosis, fibrosis, resorption, atrophy, fibrous osteodystrophy, and bone cyst) and alterations in which there is an abnormal accumulation of bone and/or osteoid because of decreased osteoclastic bone resorption or defective bone mineralization (non-proliferative hyperostosis and hyperosteoidosis).

## MORPHOLOGY

### *INFLAMMATION (Figure 1)*

Most spontaneously occurring inflammatory bone lesions in rats are due to bacterial infection and occur secondary to traumatic injuries, surgical procedures, fractures, middle ear infections, dental infections, and sinusitis. Organisms that become established in the intertrabecular myeloid tissue generally induce chronic suppurative inflammation that commonly spreads to neighboring areas. Non-infectious forms of bone inflammation also occur in rats, especially in response to treatment with certain adjuvants used to induce experimental arthritis (16,33). Modifiers can be used to describe the type of inflammation, its location, and the extent of involvement.

### *RESORPTION (Figure 1)*

Bone resorption may be abnormally accelerated under some conditions, especially near sites of inflammation. Sites of accelerated bone resorption are generally recognized by the presence of increased numbers of osteoclasts (osteoclast hyperplasia) along the resorbed surface and the presence of surface excavations giving the bone surface an irregular serrated appearance. The serrated shape is formed by the action of osteoclasts on bone, with each depression or scalloped surface representing a Howship's lacunae (resorption bay). *Dissecting osteoclasia* is a synonym that has been used to describe increased osteoclast-mediated bone resorption.

**NECROSIS (Figure 2)**

Necrosis of bone is characterized by loss of osteoblasts from bone surfaces and loss of osteocytes from lacunae. Bone necrosis is often accompanied by fragmentation of bone trabeculae and marrow necrosis. Affected bone may form sequestra that separate from surrounding bone and lie free in an abscess.

**FIBROSIS (Figure 3)**

Chronic inflammatory lesions affecting bone often heal with extensive replacement fibrosis. Fibrosis is seen as increased peritrabecular connective tissue of variable cellularity and vascularity.

**HYPEROSTEOIDOSIS (Figures 4-6)**

Osteoid is the unmineralized matrix that is deposited by osteoblasts. Hyperosteoidosis signifies an abnormal increase in non-neoplastic osteoid (30,38). In decalcified H&E-stained sections osteoid stains pink because it is rich in collagen and is uncalcified. Osteoid usually appears homogeneous (collagen fibers not visible under ordinary light) because it is rich in proteoglycans. Most cases of uncomplicated hyperosteoidosis in rats are non-proliferative and attributable to defective mineralization (osteomalacia) in which osteoid accumulates because of its resistance to osteoclastic resorption. Increased osteoid may appear as widened seams (along existing bone surfaces) and/or as a greater surface area of bone covered by osteoid. Hyperosteoidosis is commonly seen in rats given very high doses of certain bisphosphonates which may inhibit both osteoclastic resorption of pre-existing bone and mineralization of newly formed matrix, causing both hyperostosis and hyperosteoidosis, respectively. Other causes of hyperosteoidosis include aluminum toxicity, cadmium toxicity, dietary phosphorus deficiency, and vitamin D toxicity (9,21).

**FIBROUS OSTEODYSTROPHY (Figures 7 & 8)**

Fibrous osteodystrophy is a form of metabolic bone disease caused by prolonged and excessive secretion of parathyroid hormone (17). Fibrous osteodystrophy is relatively common in aged rats with chronic progressive nephropathy. It is included as a non-proliferative lesion because it is usually associated with a net decrease in mineralized bone mass in rats. In early stages of the disease osteoclastic bone resorption is accelerated, osteoclast numbers are increased, and broad surface excavations of bone are commonly observed. In later stages, bone and marrow are gradually replaced with fibrocytic cells, fibrous stroma, and increased osteoid.

**ATROPHY (Figure 9)**

Atrophy of bone refers to a decrease in the amount of bone without detectable differences from normal in the relative proportions of mineralized and non-mineralized

matrix (28). Modifiers such as generalized or localized (as might occur in an immobilized/unused limb or around severely arthritic joints) can be used to convey the extent of involvement. Atrophy results from decreased bone formation and/or increased bone resorption. Spontaneous age-related atrophy is reported to occur in rats, however, this change is not associated with spontaneous fractures (19,21). Diminished feed intake, cortisone toxicity, thyrotoxicosis, pyridoxine deficiency, heparin, B-aminopropionitrile, and dextran sulfate are also reported to result in bone atrophy (7,10,12,21,34). Use of the terms osteoporosis and osteopenia are addressed in the discussion section.

**BONE CYST (Figure 10)**

Bone cysts are rare in rats and generally appear as discrete membrane-lined, fluid-filled cavities. The classification of bone cysts reflects their diversity in form and development and is based on location, anatomic complexity, and presumed pathogenesis (17). For example, cysts may be described as subchondral if they lie beneath articular cartilage, unicameral if single chambered, or aneurysmal if blood filled and expansive. Aneurysmal bone cysts are expansive lesions that arise from disturbances in the vasculature of the bone. Subchondral pseudocysts lack a discrete lining and are frequently associated with degenerative joint disease (osteoarthritis).

**HYPEROSTOSIS, Non-proliferative (Figures 11 & 12)**

Non-proliferative forms of hyperostosis (increased non-neoplastic bone) include osteopetrosis (25) and osteopetrotic-like alterations induced by some bone-active compounds such as bisphosphonates and estrogens (21,26). The condition occurs as a result of decreased bone resorption rather than bone proliferation (17). In young (growing) rats, hyperostosis resulting from decreased bone resorption is recognized by retention (seen as lengthening) of the metaphyseal spongiosa. Osteoclasts may be decreased in number or increased in number (osteoclast hyperplasia) and hypernucleated. In older rats, medullary bone trabeculae become thickened and marrow space diminished. Differentiation from a truly proliferative change is based on the presence of increased mature lamellar bone, an absence of osteoblast proliferation, and evidence of decreased osteoclastic bone resorption.

**CARTILAGE**

Most spontaneously occurring non-proliferative cartilage lesions in rats are degenerative (24,35). Inflammatory lesions may be caused by infectious or non-infectious agents and can be induced experimentally

under a variety of conditions. The high nutritional content of modern laboratory rodent diets has virtually eliminated spontaneous nutritional diseases of cartilage (and bone); however, developmental and/or metabolic cartilage lesions can be induced experimentally by altering dietary nutrients or by administering various materials via diet or injection. Articular, growth plate, auricular, tracheal, and/or nasal cartilage may be affected and modifiers such as stifle joint, sternum, intervertebral, articular, growth plate, etc. may be needed to adequately describe the location and/or extent of involvement.

## MORPHOLOGY

### DEGENERATION

#### *Chondromucinous Degeneration (Figure 13)*

Cartilage degeneration is most commonly seen in rats as spontaneous chondromucinous degeneration (CMD) of the sternum, growth plate, and/or articular cartilage (7,15,21,35). The incidence of CMD increases with advancing age, with lesions first becoming noticeable at about 130-180 days of age (21). Incidence rates as high as 50% have been reported in some strains (35). The etiology of CMD is not known and the condition has not been reported to progress to arthritis or degenerative joint disease. CMD is generally focal but may be quite large, to the extent of causing gross enlargements, especially when the sternbrae are affected. Lesions appear as areas of necrosis within the cartilage in which chondrocytes are absent and the ground substance is fragmented. Chondrocytes at the periphery of the lesion may appear in nests or clusters, indicating attempted repair. In advanced lesions, the ground substance is lost leaving a cystic space or cavity.

#### *Degenerative Joint Disease (Figure 14)*

Cartilage degeneration also occurs as part of degenerative joint disease (DJD or osteoarthritis). DJD is reported to occur both spontaneously in Fischer 344 rats (39) and following administration of various test materials used in chronic and subchronic toxicity studies (21). The changes in the knee joint affected with DJD may vary considerably in severity. The least severe changes consist of irregularity in the contour of the articular surface, thickening of the articular cartilage, focal tinctorial changes (loss of basophilia with hematoxylin), and fibrillation of the cartilage matrix. In an attempt at repair, chondrocytes in the area proliferate, but are unable to separate and differentiate in the chondroid matrix. This latter phenomenon may explain the formation of chondrocyte clusters or clones. More severe lesions are cartilage necrosis, microfissures, subchondral bone lysis, cyst formation, synovial lining cell

hyperplasia, and thickening and ossification of the joint capsule (21).

As the articular cartilage deteriorates, the mechanical forces of weight-bearing and movement are transferred directly to the underlying subchondral bone. The underlying subchondral bone then reacts by becoming thicker and denser. In an attempt to respond to new stresses and to contain the abnormal motion, the borders of the articular surfaces undergo remodeling and extend the articular surface area. Typically this is accompanied by osteophyte formation on the peri-articular bone surfaces adjacent to or within the insertion line of the joint capsule. Chemically-induced DJD involves changes in the cartilage ground substance and may affect cartilage of the growth plate as well as that of the articular surface.

#### *INFLAMMATION (Figures 15 & 16)*

Infectious (*Mycoplasma spp.*, *Staphylococcus spp.*, etc.) or immune mediated arthritis may be experimentally induced in rats. The lesions are generally more severe than that of DJD, but some of the features are similar. A striking feature of adjuvant-induced arthritis, in contrast to DJD, is the copious inflammatory exudate in the synovial membrane and joint space (16). The thickened synovial membrane may cover the articular surfaces of the joint, a condition termed pannus, or it may undermine the cartilage by eroding subchondral bone. Osteophyte formation and ankylosis may eventually occur. Inflammation of auricular cartilage may follow placement of ear tags used for identification purposes.

#### *HYPERTROPHY (Figures 17-19)*

Hypertrophy of cartilage (especially that of the growth plate) may result from nutritional-related disturbances in mineralization (rickets) as well as from metabolic and/or chemical-related disturbances in mineralization. Defective mineralization results in a failure of vascular invasion of cartilage, which in turn results in a persistence of hypertrophied chondrocytes. The latter is generally recognized by irregular lengthening of the growth plate hypertrophied zone. Systemic defects in mineralization are invariably accompanied by the presence of increased osteoid (hyperostoidosis). Focal hypertrophy of growth plate cartilage, such as that caused by disturbances in endochondral ossification (osteochondrosis), is also reported to occur spontaneously in Sprague-Dawley rats (18).

## SYNOVIUM

Synovial lesions are generally noted in either the stifle or hock joints since these areas are the most

common joints sampled in rat toxicity studies. Inflammation is the most common non-proliferative lesion of synovium. Modifiers can be used to convey the type of inflammation, the extent of involvement, and its distribution.

## MORPHOLOGY

### *INFLAMMATION (Figures 20 & 21)*

Inflammation of the synovium is characterized by the presence of increased numbers of inflammatory cells within the synovial and subsynovial supporting tissue. Synovial lining cells may be hyperplastic or flattened and the synovial space may contain increased fluid and fibrin. Blood vessels are often congested and the supporting connective tissue may be edematous and/or may contain increased amounts of fibrous connective tissue.

## TOOTH

There are very few reports of non-proliferative tooth lesions in rats. A few examples include various studies involving high levels of sodium fluoride (8,23), vitamin A deficiency (27,32), magnesium deficiency (3–5), and altered hormone status (1,2,6,11,31). In addition, certain diets have been shown to influence the development of non-proliferative tooth lesions such as root resorption, periodontal disease, and alveolar bone resorption (13,29).

## MORPHOLOGY

### *DEGENERATION*

#### *Ameloblast Degeneration (Figures 22 & 23)*

Ameloblasts are columnar epithelial cells responsible for the production of enamel. Enamel is usually not seen in decalcified sections because it is 95% mineral and most is removed during the decalcification process. A clear vacant area, the enamel space, is usually present in place of existing enamel. Beneath the single row of ameloblasts is a stratified epithelial layer representing the remainder of the dental organ. Loss or degeneration of ameloblasts may be diffuse or focal, resulting in irregularities in the ameloblast layer. Enamel formation (or lack of formation) mirrors the changes in the ameloblasts and therefore may also appear irregular in contour. In chronic fluorosis, loss of ameloblasts may be accompanied by flattening of the underlying stratum intermedium, herniation of ameloblasts into the enamel, and inclusions of enamel in the ameloblastic layer (23).

Basophilic granules noted in fluoride treated rats are reported to represent calcium fluoride crystal formation that occurs during decalcification of tooth/bone specimens (22). Degenerative changes in ameloblasts have also been described in rats following administration of puromycin and tetracycline hydrochloride (36,37). In addition, colchicine (which disrupts microtubule formation) is reported to disrupt enamel formation and pigmentation (14).

#### *Odontoblast Degeneration (Figure 24)*

Odontoblasts are columnar mesenchymal cells that line the perimeter of the pulp cavity and are responsible for formation of dentin. A sharp line of demarcation separates the uncalcified predentin from the calcified dentin. Degeneration of odontoblasts may be subtle with minimal necrosis and/or irregularity of the dentin, or more pronounced with marked loss of odontoblasts and reduced ability to form dentin.

#### *PULP STONES (Figure 25)*

Pulp stones (single or multiple) sometimes occur within the pulp tissue and consist of concentric layers of mineralized tissue formed by surface accretion around injured or dead cells or collagen fibers. Occasionally, a pulp stone may contain tubules and be surrounded by cells resembling odontoblasts. Some pulp stones may be associated with irregularities in the contour of the dentin along the inner margin of the pulp cavity. Irregular (linear or concentric) areas of dystrophic mineralization may also occur within the pulp tissue and are referred to as false pulp stones.

#### *INFLAMMATION (Figure 26)*

Inflammation may involve the entire tooth or only certain parts such as the pulp cavity or periodontium (which consists of cementum, periodontal ligament, alveolar bone, and part of the gingiva). Inflammation of the entire tooth is commonly seen following tooth fracture and subsequent infection, especially incisors that have been trimmed because of overgrowth. Inflammation of the pulp cavity usually occurs secondary to fracture and/or inflammation in the adjacent nasal tissues or bone. Periodontitis is caused by accumulation of bacteria on the surface of the tooth and under the gingiva. The term dental plaque refers to masses of bacteria adhering to the tooth. As the bacterial plaque mineralizes, it forms what is called calculus or tartar. As the periodontal ligament is destroyed and the alveolar bone is resorbed, the gingival epithelium migrates along the root surface to form what are called periodontal pockets. Dietary factors such as fiber type and processing methods have been shown to influence the incidence and severity of periodontal disease in rats (29).

**ROOT RESORPTION (Figures 27 & 28)**

Root resorption is characterized by loss of cementum and/or dentin and is mediated by osteoclasts. Common initiating factors include malocclusion, infection, and trauma (including iatrogenic fracture). Root resorption may progress to complete loss of the tooth and replacement with fibrous connective tissue and/or bone. In other cases, root resorption may be accompanied by abnormal development of remaining viable odontogenic tissue (dental dysplasia).

**DENTAL DYSPLASIA (Figures 29 & 30)**

Incisors grow throughout life in rats. This characteristic coupled with infection, chronic inflammation, trauma, and/or fracture can result in abnormal development of odontogenic tissues. The appearance of such dysplastic lesions can vary considerably depending on the nature and extent of injury, the tissue affected, and the plane of section. Alveolar bone, cementum, dentin, enamel, and connective tissue resembling that of the dental papilla may develop in various combinations and abnormal patterns. In most cases, however, the tooth socket becomes filled with large irregular masses of dentin-like material surrounded by fragments of the original tooth and islands of bone. Tooth-like structures (denticles) with tissue resembling the dental papilla may also form, but tend to remain relatively small and solitary.

**INCISOR OVERGROWTH (Figure 31)**

If rats do not properly wear their teeth by gnawing, or if the incisors are maloccluded, then overgrowth may occur. Incisor overgrowth may result in decreased feed intake, inanition, penetration of teeth into opposing tissues, and even death.

**DISCUSSION**

Inflammation of bone is commonly associated with increased bone resorption at the margin of the lesion. This may give rise to a compensatory hyperostotic response along more distant viable trabeculae in an attempt to wall-off the inflammation and/or compensate for mechanical instability. Eventually, the area of inflammation may become enclosed by a shell of bone and mature fibrous connective tissue. Large amounts of hyperostotic bone may result in radiographic sclerosis (33). Use of terms such as osteitis, osteomyelitis, and arthritis is not recommended because most computerized pathology data tables are organized by organ system, which precludes the need for terminology indicating organ specific inflammation.

Hyperosteoidosis is also a common feature of

proliferative hyperostotic alterations because the rate of osteoid production is increased and/or the number of formation surfaces is increased. However, when increased osteoid is present as part of a hyperostotic condition it should not be split-out as a separate diagnosis unless the amount of osteoid is beyond what would normally be expected for the condition under examination. Use of the term osteomalacia is not recommended because it implies that there is prolongation of the mineralization lag time, which can only be confirmed by special bone labeling techniques. In decalcified sections, osteoid (unmineralized matrix) can usually be differentiated from bone (mineralized matrix) based on differential staining qualities, however, in some specimens the two may be difficult to differentiate without using special undecalcified histologic techniques.

Use of the term osteoporosis is not recommended over the term atrophy because its meaning is controversial. Some scientists use the two terms as synonyms, yet others use the term osteoporosis to communicate a more specific meaning such as a clinical condition associated with a generalized age and/or hormone-related loss of bone mass. Use of the term osteopenia is not recommended because it denotes a non-specific decrease in bone mass that could be caused by a variety of disease states including atrophy, fibrous osteodystrophy, and hyperosteoidosis.

There may be difficulty in determining if an abnormal increase in non-neoplastic bone (hyperostosis) is due to increased bone formation or decreased bone resorption, especially when limited to examining single time-point decalcified bone sections. Most errors in interpretation are made when young rats are given compounds that inhibit osteoclastic bone resorption, resulting in modeling defects and increased metaphyseal bone. Interpretation of such alterations requires judgment based on experience and all other pertinent information that is available. The key is to recognize the alteration as a defect in resorption and not to over-interpret the increase in bone mass as a proliferative alteration.

Spontaneous hyperostotic alterations resembling osteopetrosis are occasionally seen in aged F344 rats, especially females. The terms osteosclerosis and osteopetrosis have been used to describe similar age-related increases in non-neoplastic bone mass (40). Use of the term osteopetrosis is not recommended unless it is known that there is a genetic and/or hereditary basis for the decreased osteoclast function. The term osteosclerosis should be reserved for describing radiographic increases in bone density.

The term "rickets" refers to the growth plate manifestation of a generalized defect in mineralization. The histologic hallmark of rickets in rats is a persistence of hypertrophied chondrocytes resulting in a lengthened

growth plate. The term "hypertrophy" with appropriate modifiers (such as growth plate) is recommended for describing such alterations because it is descriptive, it doesn't require demonstration of defective mineralization of cartilage (which is difficult to impossible to confirm in decalcified sections), and because the term can be applied to non-growth plate cartilage that may be similarly affected.

The term dental dysplasia is included as a non-proliferative lesion because it represents abnormal development of injured and/or displaced odontogenic tissue. In some cases, however, dysplastic dental lesions progress to proliferative lesions that expand beyond the borders of the alveolus and exhibit cytologic overlap with odontomas. Like compound and complex odontomas, such lesions are not considered neoplasms, but hamartomas and represent focal malformations that resemble neoplasms but result from faulty organ development. In contrast, ameloblastic odontomas are considered true neoplasms. Differentiating dental dysplasia from odontoma in rats is problematic and this is underscored by a report claiming experimental induction of odontomas in rats by traumatic injury (20). In general, the term odontoma should be reserved for large masses that have proliferated well beyond all margins of the alveolus, compress surrounding tissue, and contain multiple denticle-like structures or large disorganized masses of dentin, enamel, and connective tissue resembling pulp mesenchyme and/or the dental papilla.

**RECOMMENDED  
NOMENCLATURE AND  
DIAGNOSTIC CRITERIA  
FOR NON-PROLIFERATIVE LESIONS OF  
BONE, CARTILAGE, TOOTH, AND  
SYNOVIUM IN RATS**

**BONE**

**INFLAMMATION**

1. Increased numbers of inflammatory cells in and around bone tissue

**RESORPTION**

1. Increased numbers of osteoclasts and resorption bays along bone surfaces

**NECROSIS**

1. Loss of osteoblasts from bone surfaces and/or loss of osteocytes from lacunae
2. May be accompanied by fragmentation of bone trabeculae and marrow necrosis

**FIBROSIS**

1. Increased fibrous connective tissue of variable cellularity and vascularity in and around bone tissue

**HYPEROSTEOIDOSIS**

1. Increased non-neoplastic osteoid (unmineralized bone matrix)

**FIBROUS OSTEODYSTROPHY**

1. Increased osteoclastic excavation of bone
2. Replacement of bone and marrow with fibrous stroma and osteoid

**ATROPHY**

1. Decreased amount of bone
2. Normal relative proportions of mineralized and non-mineralized matrix
3. Generalized or localized

**CYST**

1. Osteolytic fluid-filled cavity
2. Cavity may be expansive and contain blood, fibrous trabeculae, and osteoclastic giant cells
3. Cavity may be surrounded by a shell of lamellar and/or woven bone

**HYPEROSTOSIS (Non-proliferative)**

Young rats:

1. Lengthening and retention of the metaphyseal spongiosa
2. Osteoclasts may be increased in number and hypernucleated, decreased in number, or normal in number (depends on cause)

Mature rats:

1. Trabeculae thickened with increased mature (lamellar) bone
2. Decreased numbers of osteoclasts and/or resorption bays
3. Absence of osteoblast proliferation

**CARTILAGE**

**DEGENERATION**

**Chondromucinous Degeneration**

1. Focal lysis of cartilage ground substance and chondrocyte necrosis
2. Leads to cystic lesion in cartilage

3. Especially common in sternbrae
4. May involve articular and/or physal cartilage

#### ***Degenerative Joint Disease***

1. Irregular thickening (early stage) and erosion (late stage) of articular cartilage
2. Cloning of chondrocytes and irregular loss of matrix basophilia
3. Fibrillation of articular cartilage, sometimes accompanied by subchondral cyst formation
4. Thickening of the synovial membrane with hypertrophy and hyperplasia of synoviocytes
5. Joint capsule thickening and ossification in late stage
6. If cause is chemical change in ground substance, then may also affect growth plate cartilage

#### ***INFLAMMATION***

1. Increased numbers of inflammatory cells in and around cartilage tissue

#### ***HYPERTROPHY***

1. Abnormal retention or persistence of well differentiated chondrocytes (especially growth plate)

### **SYNOVIUM**

#### ***INFLAMMATION***

1. Increased numbers of inflammatory cells within synovial tissue

### **TOOTH**

#### ***DEGENERATION***

##### ***Ameloblast Degeneration***

1. Focal or diffuse necrosis and/or atrophy of ameloblasts
2. May be associated with irregularities in the contour of the enamel
3. Enamel may be diminished in amount (difficult to determine in decalcified sections)

##### ***Odontoblast Degeneration***

1. Focal or diffuse necrosis and/or atrophy of odontoblasts
2. May be associated with irregularities in the contour of the dentin

#### ***PULP STONES***

1. Clusters or nests of dentin or dentin-like material in the pulp cavity
2. May contain tubules and be surrounded by cells

resembling odontoblasts

3. May be associated with irregularities in the contour of the dentin
4. Irregular (linear or concentric) areas of dystrophic mineralization are referred to as false pulp stones

#### ***INFLAMMATION***

1. Increased numbers of inflammatory cells within the pulp cavity and/or periodontium
2. Commonly seen following fracture and/or infection of incisors
3. May be accompanied by a nasal cavity lesion or inflammation in adjacent bone

#### ***ROOT RESORPTION***

1. Loss of cementum and/or dentin
2. May be accompanied by inflammation and/or fracture
3. May progress to complete loss of the tooth and replacement with fibrous connective tissue and/or bone
4. May be accompanied by abnormal development of remaining viable odontogenic tissue (dental dysplasia)

#### ***DENTAL DYSPLASIA***

1. Aberrant development of odontogenic tissues
2. Tooth socket commonly becomes filled with large irregular masses of dentin-like material surrounded by fragments of the original tooth and small islands of bone
3. If not destroyed, displaced odontogenic tissues may form denticle-like structures
4. Most commonly seen in incisor teeth
5. Usually associated with injury/fracture and/or infection and displacement of odontogenic tissues
6. May exhibit cytologic overlap with odontoma

#### ***INCISOR OVERGROWTH***

1. Abnormal elongation of incisors

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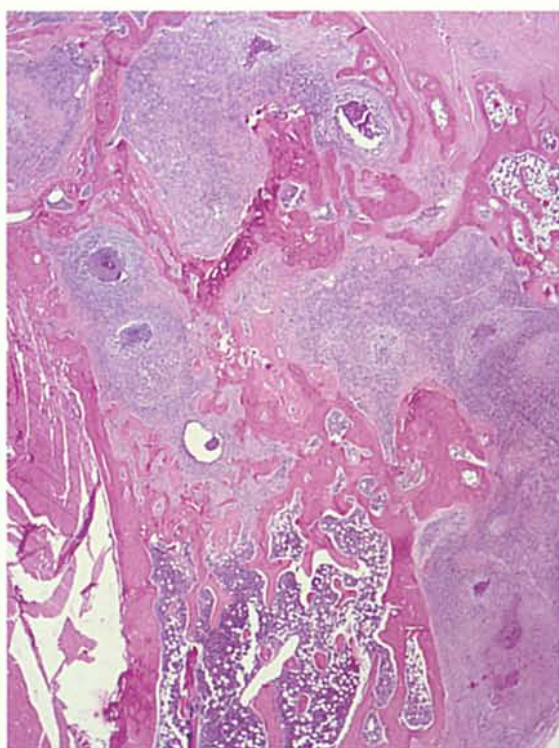
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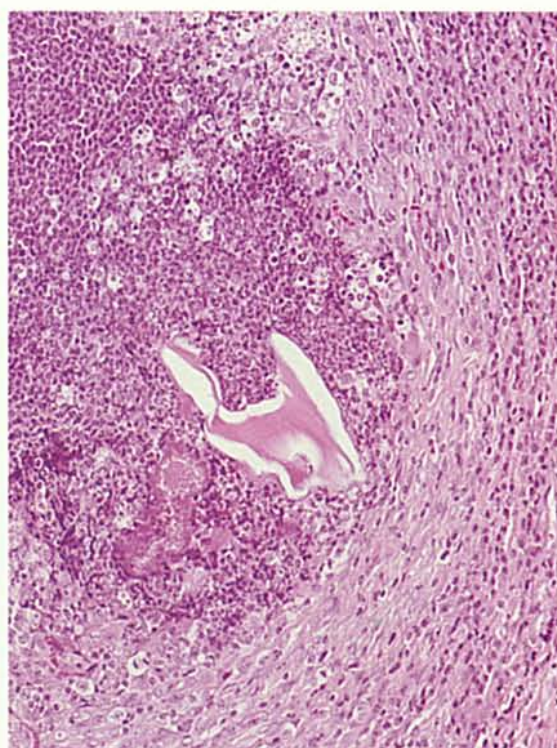
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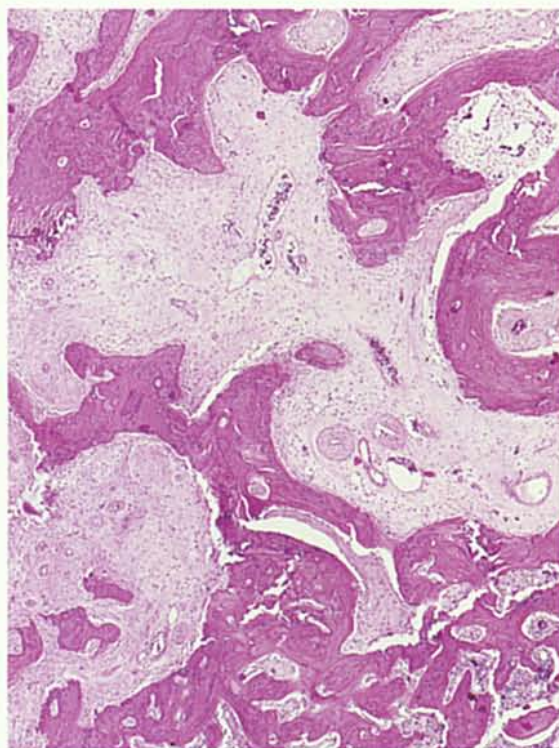
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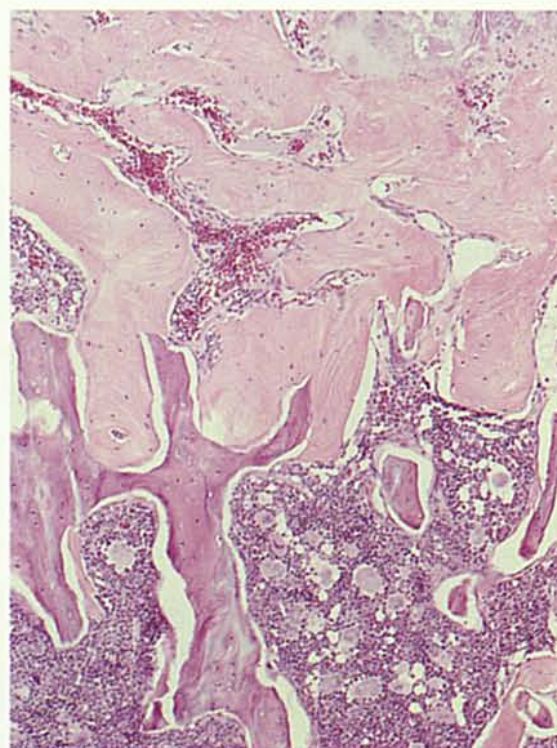
**Fig. 1 – Bone, inflammation and resorption.** Post-surgical bacterial infection involving proximal tibia. Also, note extensive necrosis (H&E).



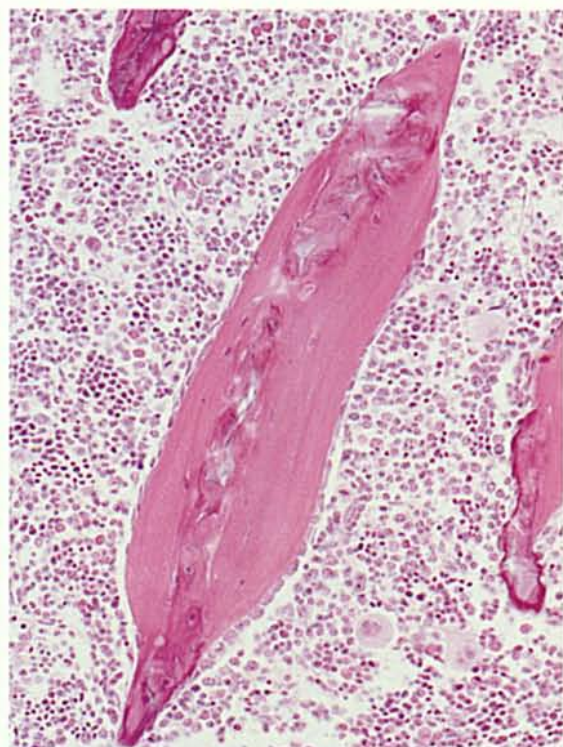
**Fig. 2 – Bone, necrosis and inflammation.** Necrotic bone fragment (sequestrum) surrounded by inflammatory cells (H&E).



**Fig. 3 – Bone, fibrosis.** Increased fibrous connective tissue (scarring) accompanying a proliferative hyperostotic alteration in response to a bacterial infection (H&E).



**Fig. 4 – Bone, hyperosteoidosis.** Increased non-neoplastic osteoid in a decalcified section from a mature rat treated with a crystal growth inhibitor (H&E).



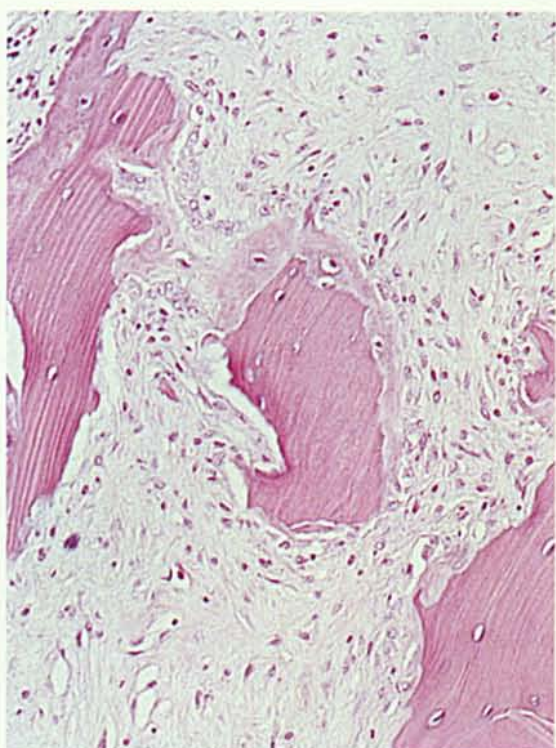
*Fig. 5 – Bone, hyperosteoidosis. Increased non-neoplastic osteoid in an undecalcified section from a young rat treated with a crystal growth inhibitor (H&E).*



*Fig. 6 – Bone, hyperosteoidosis. Serial section from same bone spicule shown in Fig. 5 (von Kossa-Toluidine Blue).*



*Fig. 7 – Bone, fibrous osteodystrophy. Increased osteoclastic excavation of bone cortex and replacement with fibrous connective tissue (H&E).*



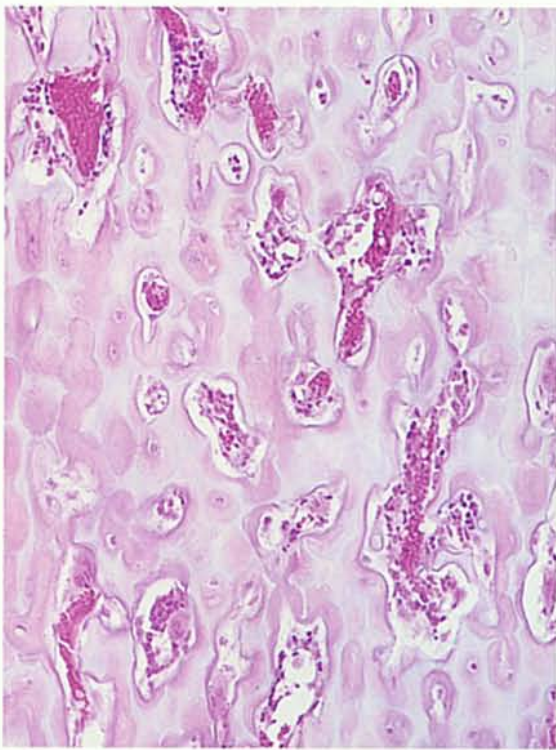
*Fig. 8 – Bone, fibrous osteodystrophy. Higher magnification of Fig. 7 showing increased osteoclastic excavation of bone, replacement of bone with fibrous stroma and osteoid (H&E).*



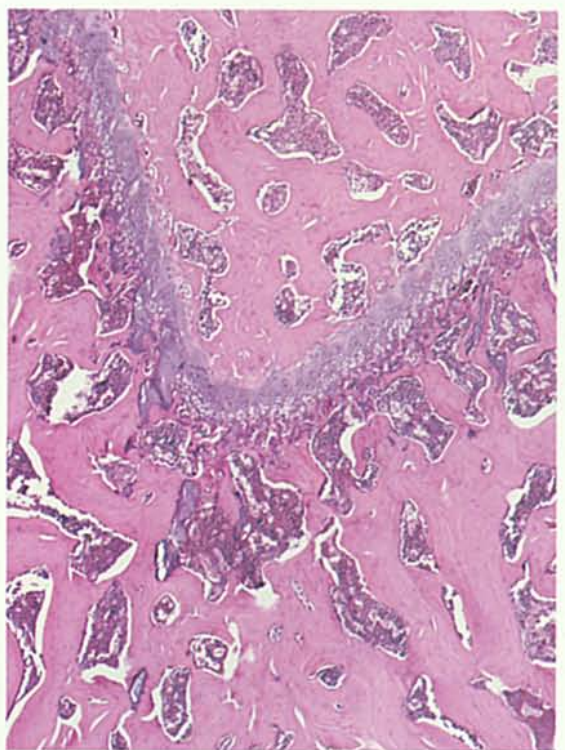
**Fig. 9** – Bone, atrophy. Decreased epiphyseal and metaphyseal bone mass (H&E).



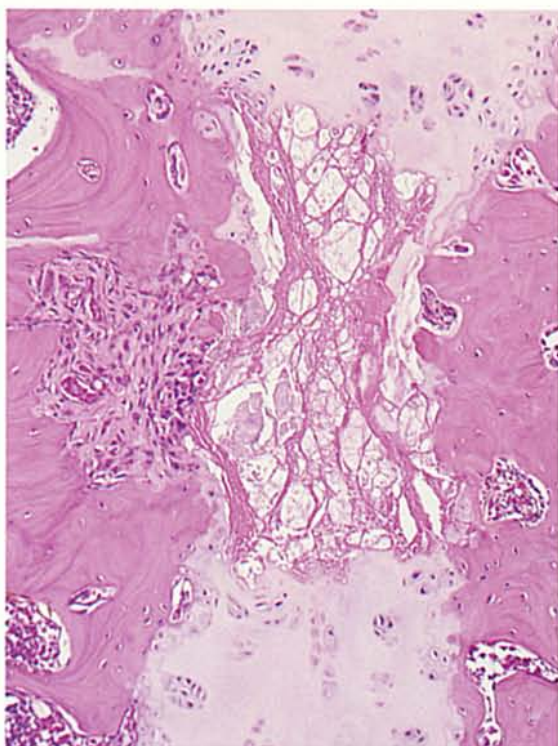
**Fig. 10** – Bone, cyst (aneurysmal). Expansive osteolytic lesion with discrete blood-filled cavity (H&E). Reprinted with permission of Academic Press (21).



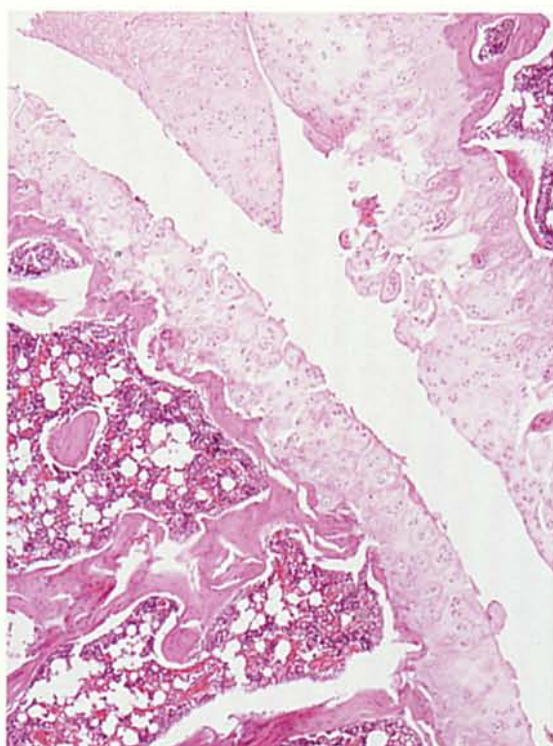
**Fig. 11** – Bone, hyperostosis, non-proliferative (young rat). Retention of metaphyseal spongiosa (H&E).



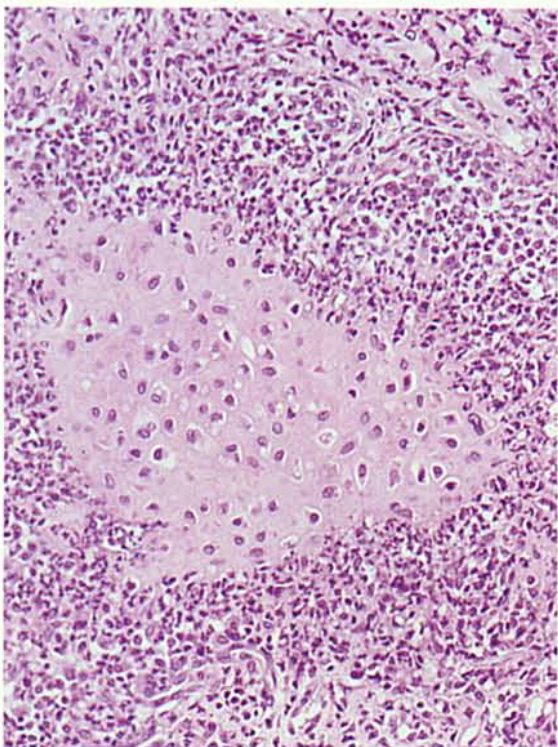
**Fig. 12** – Bone, hyperostosis, non-proliferative (mature rat). Excessive thickening of epiphyseal and metaphyseal bone trabeculae (H&E). Reprinted with permission of Academic Press (21).



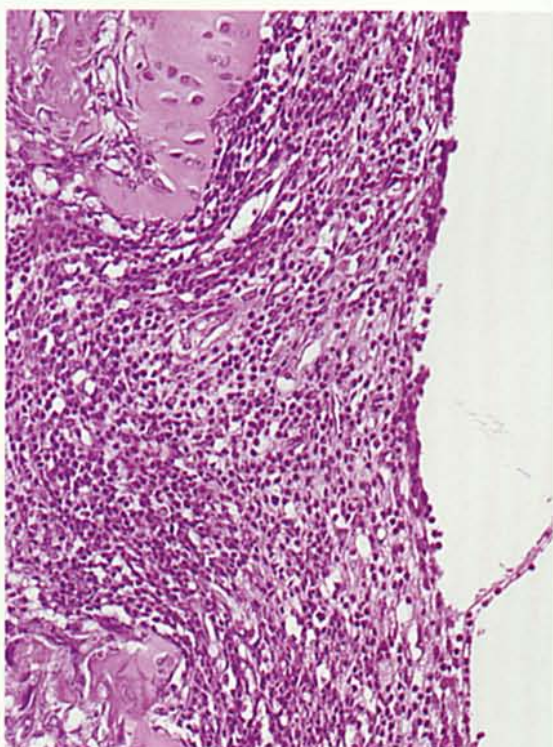
**Fig. 13 – Cartilage, chondromucinous degeneration.** Focal degeneration of cartilage with loss of chondrocytes and formation of cystic space containing eosinophilic fibrillar material (H&E).



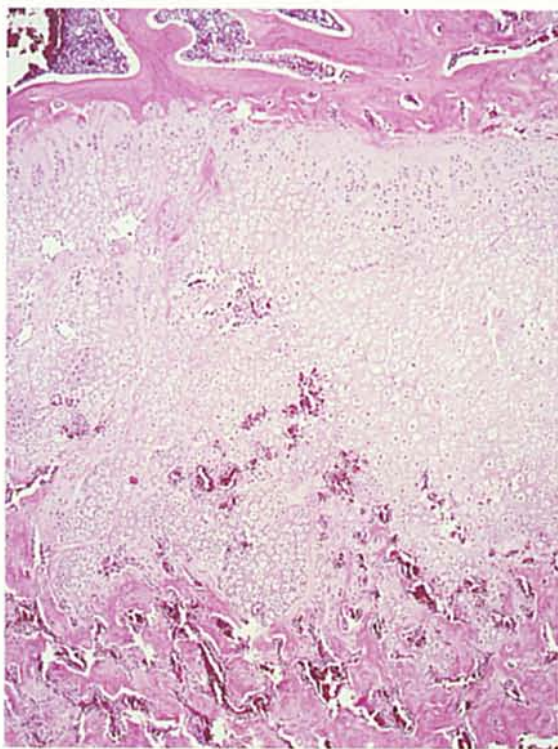
**Fig. 14 – Cartilage, degenerative joint disease.** Note microfissures in articular cartilage and nesting of chondrocytes (H&E).



**Fig. 15 – Cartilage, inflammation (ear).** Chronic suppurative inflammation (and cartilage hyperplasia) following placement of a metal identification tag (H&E).



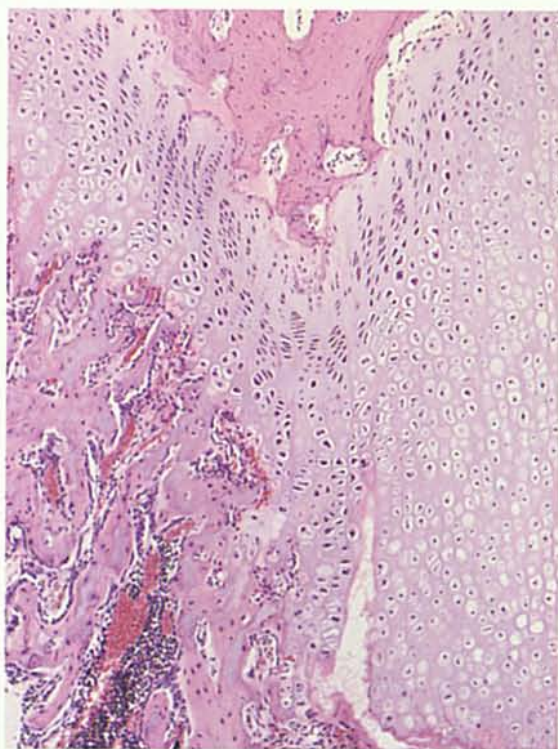
**Fig. 16 – Cartilage, inflammation (tarsal joint).** Chronic suppurative inflammation of articular cartilage (with perforation) in a rat with adjuvant-induced arthritis (H&E).



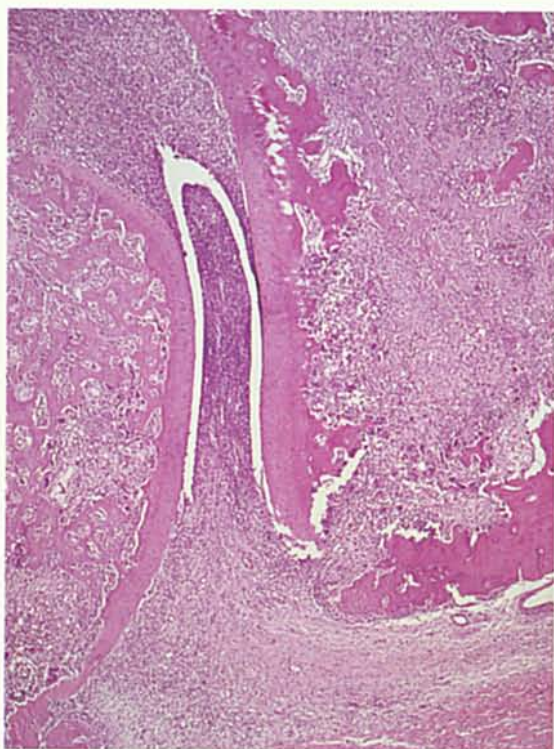
**Fig. 17 – Cartilage, hypertrophy.** Persistence of hypertrophied chondrocytes in a rat fed a diet deficient in phosphorus and vitamin D (decalcified H&E).



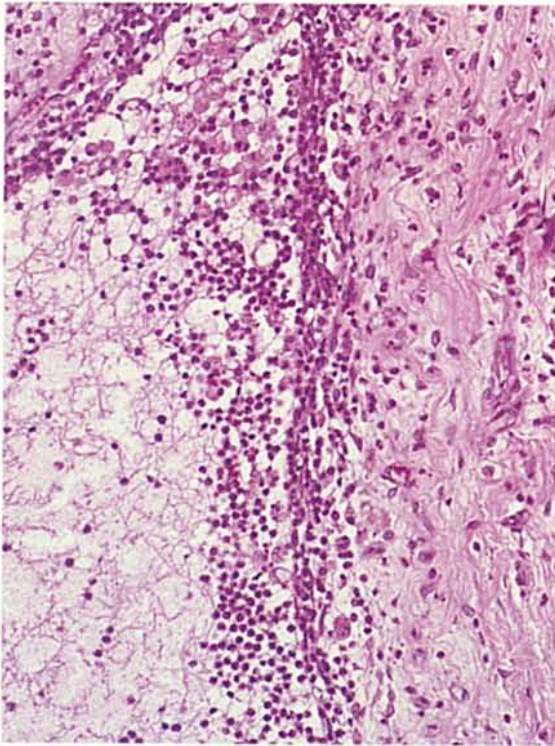
**Fig. 18 – Cartilage, hypertrophy.** Persistence of cartilage in a young rat given a crystal growth inhibitor. Note defective mineralization of cartilage and bone (undecalcified von Kossa-acid fuchsin).



**Fig. 19 – Cartilage, hypertrophy.** Focal persistence of hypertrophied chondrocytes (decalcified H&E).



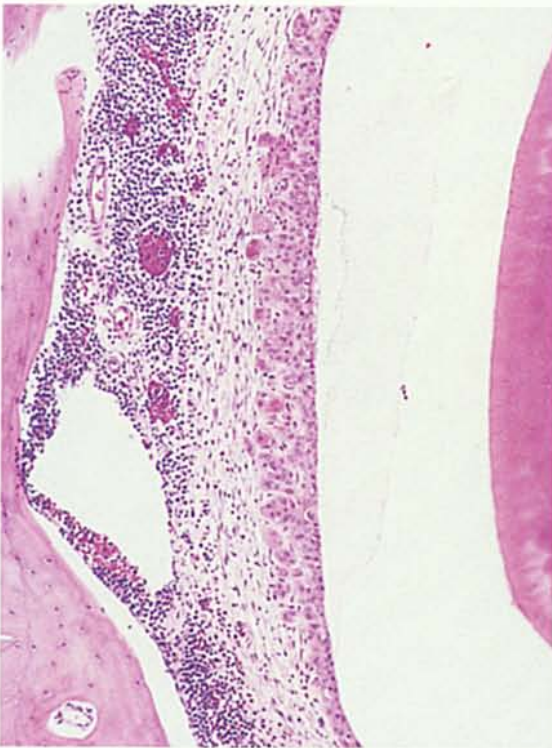
**Fig. 20 – Synovium, inflammation.** Pannus in a rat with adjuvant-induced arthritis. Note thickened synovium, exudate covering articular cartilage, and invasion of subchondral bone (H&E).



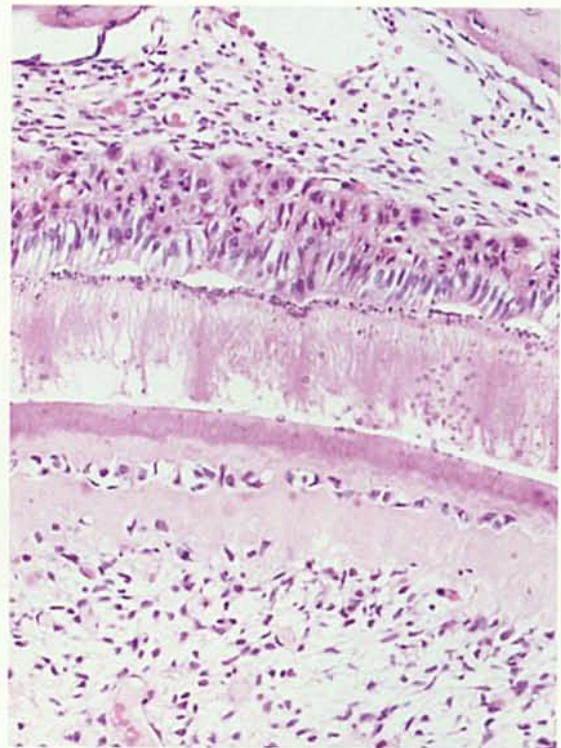
**Fig. 21** – Synovium, inflammation. Suppurative synovial exudate in a rat with adjuvant-induced arthritis. Note neutrophils in joint space. Synovial lining cells are flattened (H&E).



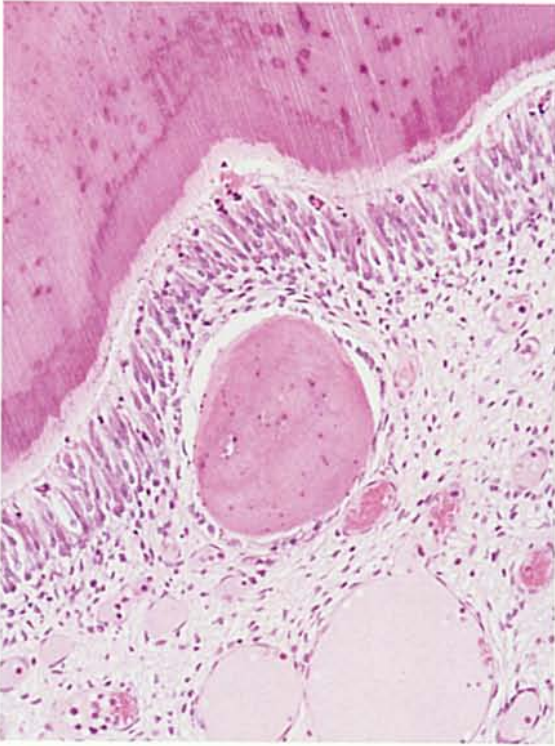
**Fig. 22** – Tooth, ameloblast degeneration. Irregular ameloblast degeneration in a rat treated with NaF. Note how enamel contour mirrors distribution of ameloblast degeneration (incompletely decalcified H&E).



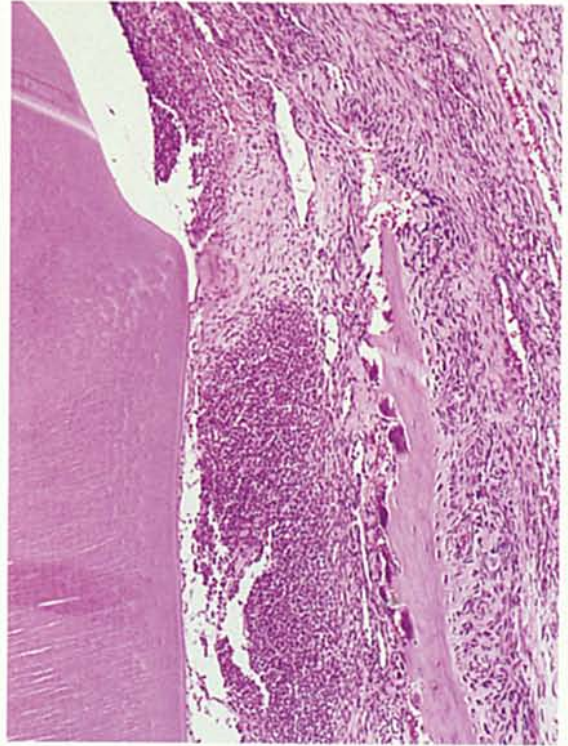
**Fig. 23** – Tooth, ameloblast degeneration. Severe ameloblast degeneration in a rat treated with high levels of NaF. Clear enamel space is produced by complete decalcification. Inflammation is also present (H&E).



**Fig. 24** – Tooth, odontoblast degeneration. Severe odontoblast degeneration and mild ameloblast degeneration in a rat treated with NaF (H&E).



**Fig. 25 – Tooth, pulp stone.** Island of dentin-like material in pulp tissue (H&E).



**Fig. 26 – Tooth, inflammation.** Inflammation of periodontal ligament space with evidence of both increased alveolar bone formation and resorption (H&E).



**Fig. 27 – Tooth, root resorption.** Root (R) is largely resorbed and replaced with fibrous connective tissue. Also note early in-growth of alveolar bone (arrows).



**Fig. 28 – Tooth, root resorption and dental dysplasia.** Root is replaced with fibrous connective tissue and islands of bone. Dysplastic lesion appears as a very small malformed tooth (T) with enamel space (arrow).



**Fig. 29** – Tooth, dental dysplasia. Tooth socket is partly filled with a large irregular mass of dentin-like material (D) surrounded by bone (B) and fragments (F) of the original tooth.



**Fig. 30** – Tooth, dental dysplasia. Tooth socket is filled with a large irregular mass of dentin-like material (D) accompanied by aberrant development of tissue resembling the dental papilla (P).



**Fig. 31** – Tooth, incisor overgrowth. Upper incisors are beginning to grow into the hard palate.