

# Proliferative Lesions of Bone, Cartilage, Tooth, and Synovium in Rats

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## BONE

### INTRODUCTION

Establishing guidelines for the standardization of terminology and diagnostic criteria for proliferative bone alterations in rats requires a clear understanding of how the term "proliferative" is to be applied to bone. Included under the proliferative bone "umbrella" are all bone neoplasms and those non-neoplastic bone alterations in which there is an abnormal increase in bone mass attributable to increased matrix formation and/or bone cell proliferation. Excluded from the proliferative category are those bone alterations in which there is an abnormal increase in bone mass attributable to defective osteoclastic bone resorption and/or mineralization, as observed in some developmental disorders and certain chemically-induced defects in bone resorption/mineralization. The latter will be addressed in a subsequent guide on the terminology and diagnostic criteria for nonproliferative bone lesions in rats.

To achieve standardization of diagnostic terminology, the use of synonyms or terms that are commonly used to describe the same alteration must be avoided and diagnostic criteria must be clearly defined. This is especially important in regard to the terminology used to identify non-neoplastic proliferative bone lesions, because it is currently very arbitrary and inconsistent. For

example, a proliferation of non-neoplastic subperiosteal bone is commonly referred to as "hyperostosis," "bone hyperplasia," "new bone growth," "reactive bone growth," "bone proliferation," "exostosis," and "osseous hyperplasia." The use of such similar terms to describe the same alteration impairs communication and makes comparison and interpretation of different data bases of uncertain value. The benefit of standardizing terminology is that it will significantly improve the consistency of toxicologic pathology data and thus facilitate communication among toxicologic pathologists.

In contrast, the terminology used to identify neoplastic bone alterations is relatively consistent. However, bone tumors are often challenging to accurately diagnose because of their rarity in rats (which limits the advantage of personal experience) and because they may appear in disguised form. In addition, some hyperostotic lesions can be difficult to distinguish from bone neoplasia. Our purpose is to identify proliferative bone lesions in rats using broadly recognized terminology and to summarize the histologic features that characterize these proliferative bone lesions using widely accepted diagnostic criteria.

### MORPHOLOGY

#### *HYPEROSTOSIS (Figures 1-6)*

Hyperostosis is defined as hypertrophy of bone, an abnormal increase in non-neoplastic skeletal bone mass

(38). Hyperostoses may be proliferative or non-proliferative, depending on the mechanism by which the increase in bone mass occurs. Increased bone mass that forms as the result of increased bone formation and/or bone cell proliferation is considered proliferative. In contrast, increased bone mass that forms as the result of decreased bone resorption and/or defective or delayed mineralization is considered nonproliferative. The term “hyperostosis” is recommended as a “catch-all” term for those non-neoplastic increases in bone mass that are proliferative but cannot be identified as a specific diagnostic entity and those non-neoplastic increases in bone mass for which the mechanism of the increase is unclear.

An example of the latter is a proliferative hyperostotic alteration that diminishes over time and is no longer an active proliferative lesion. Such alterations appear nonproliferative, because what was once highly cellular woven bone has been converted to lamellar bone, bone surfaces are lined by a single uniform layer of flattened osteoblasts, and the intertrabecular stroma consists of fat or hematopoietic tissue. If followed over a long enough period of time, most non-neoplastic proliferative bone alterations would eventually appear nonproliferative. This behavior is a reflection of their non-neoplastic nature.

Hyperostoses usually form along pre-existing bone surfaces or “envelopes” (periosteal, endocortical, and trabecular) and they may be focal, multifocal, or diffuse and composed of woven and/or lamellar bone (45). Demarcations between normal bone and affected areas are not always distinct. Additional modifiers such as epiphyseal, metaphyseal or diaphyseal may be needed to adequately convey the area and extent of involvement. Several subtypes of hyperostosis exist, including “exostosis” (periosteal hyperostosis), “enostosis” (endosteal hyperostosis), and “osteosclerosis” (trabecular hyperostosis resulting in increased bone density without alteration in the shape of the affected bone) (45). Use of these latter terms in toxicologic pathology data tables, however, is not recommended in order to assure consistency in terminology. In place of these terms the anatomic location of the hyperostosis should be identified using appropriate modifiers.

The histologic features of hyperostoses vary with the age of the lesion and they are influenced by complicating factors such as inflammation. Key histologic features of typical proliferative hyperostoses include the presence of woven and/or lamellar bone that forms in an organized interconnected trabecular networking or “looping” pattern, osteoblast “rimming” of osteoid/bone spicules (where bone surfaces are lined with a uniform layer of plump active-appearing osteoblasts that maintain normal polarity along the trabecular margin), and the presence of a hypocellular but vascular intertrabecular stroma. Newly formed or immature/primitive proliferative hyperostoses may appear atypical, because the osteoid is present in small isolated islands, there is an absence of trabecular networking,

osteoblast rimming is indistinct, and the intertrabecular stroma is highly cellular. Variable features include inflammation and the presence of tissues other than bone, including cartilage, osteoid, fibroblasts, and giant cells. These variable features may become prominent in hyperostoses associated with trauma, radiation, and local invasion of non-osseous tumors, making differentiation from primary bone tumors difficult.

#### ***CALLUS (Figure 7)***

A callus is a form of hyperostosis in repair of a bone fracture. The histologic features of a callus are influenced by mechanical and metabolic factors and they vary with the age of the callus (14). In general, a callus exhibits a zonation phenomenon in which bone matrix production begins at the periphery and spreads inward toward a more immature central fibroblastic core. Early stages consist of hemorrhage, fibrin exudation, and necrosis, followed by proliferation of fibroblastic mesenchymal cells. The mesenchymal cells gradually appear more numerous and pleomorphic, with large nuclei and frequent mitotic figures, and they may appear to permeate muscle. The mesenchymal cells differentiate into woven bone and/or primitive cartilage, which is gradually replaced by bone (endochondral bone formation). Concurrently, woven bone forms in areas where the periosteum is intact and in the medullary canal without passing through an intermediate stage of cartilage formation (intramembranous bone formation). In the later stages there is greater trabecular networking, the marrow becomes hypocellular, osteoblasts become flattened, and woven bone is replaced with lamellar bone during subsequent remodeling.

#### ***OSTEOPHYTE (Figure 8)***

An osteophyte is a periarticular hyperostotic alteration accompanied by degenerative joint disease and/or displacement of the perichondrial ring (layer of chondroprogenitor cells that surround the growth plate) (23). “Immature” forms may be extensively cartilaginous or may have a cartilage cap that is partly replaced by bone in a manner analogous to endochondral ossification. Mature forms consist of a shell of lamellar bone and a core of marrow without a cartilage cap. Osteophytes are differentiated from other hyperostoses and osteochondromas by their periarticular location and the presence of degenerative joint disease.

### ***FIBRO- AND CHONDRO-OSSEOUS METAPLASIA (Figures 9, 10)***

Fibro-osseous and chondro-osseous metaplasia occur when fibroblastic tissue is stimulated or induced to form non-neoplastic bone and/or cartilage (25). The new bone forms with or without a cartilage template and is partly bordered by fibroblastic tissue. Osseous metaplasia may occur in injured/inflamed soft tissues (especially the pinna of ear-tagged rats), hyperostoses, and in tumors. A variety of cells and agents can induce fibroblastic tissue to form cartilage and/or bone matrix. Even some epithelial tumors can induce osteoid and/or bone formation. In the latter situation, careful examination of the bone-tumor interface is required to determine if matrix is being formed by neoplastic cells or by fibroblasts undergoing metaplastic transformation.

### ***OSTEOCHONDROMA (Figure 11)***

Osteochondromas are expansile osseous tumors that arise from the external bone surface. They consist of an outer rim of proliferating growth plate-like cartilage that undergoes endochondral ossification, resulting in an inner zone of lamellar bone trabeculae separated by abundant marrow fat and hematopoietic tissue (9,42). Bone trabeculae are lined with a uniform population of flat osteoblasts and the marrow cavity of the tumor may be seen to communicate with that of the parent bone. Osteochondromas are not associated with degenerative joint disease or displacement of the perichondrial ring.

### ***OSTEOMA (Figures 12, 13)***

Osteomas are expansile tumors that generally arise from the bone surface (18). They are variable in size, with smooth but undulating contours. Some osteomas may have a pedunculated appearance. Osteomas are composed of very dense bone (almost solid appearing) that is predominantly lamellar (but may be a mixture of woven and lamellar bone). Immature osteoid-rich trabeculae (if present) are located peripherally and may show osteoblast rimming. Mature trabeculae, rich in dense bone, may lack rimming altogether and many osteocyte lacunae may be empty. The intertrabecular stroma is generally sparse, but may contain marrow elements.

### ***OSTEOSARCOMA (Figures 14-18)***

Osteosarcomas arise from both skeletal and extraskeletal sites and are generally invasive and highly destructive (18,20,22,31,41). In control Fischer 344 rats,

the average incidence of skeletal osteosarcomas is 0.5%, with a range of 0.0 to 6.0% (2). A study of the skeletal distribution of twenty-six spontaneous skeletal osteosarcomas in a large population of Wistar-derived control rats revealed that males were affected about twice as frequently as females and that the site of origin of most osteosarcomas was the vertebral column (41). A variety of agents (chemicals, metals, and viruses) have been shown to be capable of inducing osteosarcomas in rats; however, these agents are either not naturally occurring or they must be injected/implanted directly into bone in order to induce tumor formation (27).

Regardless of the site of origin, the osteosarcoma can assume more variable histologic features and a greater range of anaplasia than any other bone tumor, resulting in numerous histologically confusing patterns. Multiple subtypes have been recognized in rats, including osteoplastic, osteoblastic, fibroblastic, telangiectatic, and compound (18). Most osteosarcomas demonstrate high-grade anaplasia, a high mitotic index, and metastasis to the lungs is common. The histologic hallmark of an osteosarcoma is the production of osteoid by malignant stromal cells. Osteosarcomas in rats are not capable of producing mature (lamellar) bone. Variable features include the formation of cartilage, fibroblastic connective tissue, large vascular spaces, osteoclast-like giant cells, periosteal hyperostosis, and necrosis. These variable features usually represent reactive or degenerative changes; however, neoplastic cartilage and fibroblastic tissue may be present in osteosarcomas.

Osteosarcomas generally exhibit a zonation phenomenon where "older" (more productive) cells are central and "younger" (less productive) cells are peripherally located. Most tumor bone and osteoid are centrally placed and cells at the periphery may show little evidence of osteoid or woven bone production. Osteosarcomas may be encased by a peripheral border of periosteum. With time, the tumor cells will infiltrate between host bone trabeculae, forming what is called a permeative pattern at the lesion host-bone interface, sometimes with trapping of mature trabecular bone and immature hyperostotic periosteal bone. Organized looping or networking of tumor bone trabeculae are not seen in conventional osteosarcomas. Osteoblasts may be aligned along the periphery of trabeculae, but alignment is not continuous and cells point in all directions without normal polarization.

## **DISCUSSION**

Most hyperostotic bone alterations are the result of proliferative bone activity. Exceptions include hyperostotic bone alterations that result from delayed or defective bone resorption and/or mineralization. These

latter alterations still fall within the definition of hyperostosis; however, when identified as being due to defective resorption, the term "hyperostosis" should be qualified by the modifier "nonproliferative" or "osteopetrotic" to distinguish the alteration from a truly proliferative change. In young rats, retention of metaphyseal spongiosa with prominent cartilage cores is diagnostic of defective osteoclastic resorption. In adult rats, differentiating mature proliferative hyperostosis from nonproliferative hyperostosis can be more challenging, especially if cellular activity has subsided and evaluation is limited to a single time-point of decalcified bone section. In some cases, proliferative and non-proliferative hyperostoses may coexist in the same animal. Interpretation of such alterations requires judgment based on experience and all other pertinent information that is available.

Hyperosteoidosis is a related term that refers to an abnormal increase in non-neoplastic osteoid (unmineralized bone matrix that is deposited by osteoblasts) (32,45). In H&E-stained sections, osteoid generally is homogeneously stained 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; however, osteoid that is proteoglycan-poor may have visible collagen fibers. Ultrastructurally, osteoid contains matrix vesicles. Substances that are commonly confused with osteoid include fibrin, ordinary collagen, and chondroid (24). Fibrin is usually present in areas of hemorrhage and fibers are not visible when viewed with polarized light. Collagen deposited by fibroblasts has visible collagen fibers when viewed under ordinary light conditions, because it has less proteoglycans than osteoid. Chondroid is a primitive form of cartilage that is rich in collagen. Chondroid stains as pink as osteoid, but is typically more rounded (smooth margins), more homogeneous, it usually contains more obvious perilacunar cartilage cell-like spaces, and it is usually not associated with conversion to woven bone (24).

Hyperosteoidosis is commonly seen in proliferative hyperostotic alterations because the rate of osteoid production is increased and/or the number of formation surfaces is increased. 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. Most cases of pure hyperosteoidosis in rats are non-proliferative and attributable to defective mineralization (osteomalacia) in which osteoid accumulates because of its resistance to osteoclastic resorption.

In some instances, sarcomas other than osteosarcomas may be associated with osteoid and/or bone production. In these cases the new bone is not malignant and is not

produced by the malignant cells per se, but by periosteal cells or trapped host fibroblastic mesenchyme that is stimulated to produce osseous elements. The osseous tissues merely represent a form of abnormal callus or atypical hyperostosis. Atypical hyperostotic matrices, especially if newly formed, can lead to considerable dilemma as to which matrix is produced by the tumor itself and which is a reaction to the tumor. Most atypical hyperostotic matrices are caused by periosteal reaction, fracture, response to infection, metastasis, or exogenous agents such as radiation (20). Atypical hyperostotic osteoid/bone is characterized by the presence of increased numbers of plump osteoblasts and fibroblasts with large nuclei lacking in atypical mitoses, focal osteoblastic rimming of the osteoid, and proximity to a bone surface.

## CARTILAGE

### INTRODUCTION

The histogenesis and anatomy of cartilage in the rat are essentially the same as in other vertebrates. Cartilaginous tissues are found throughout the rat's musculoskeletal system, especially at articular surfaces, synchondroses, sites of endochondral ossification, and extensions of bony structures such as ribs. Cartilage also provides structural rigidity in non-skeletal tissues such as the ear, nasal cavity, trachea, and lung. The growth plates (physes) of long bones in rats do not completely resorb after maturity, maintaining some residual growth plate cartilage throughout life.

Primary neoplastic lesions of cartilage in rats are rare. Chondromas and chondrosarcomas in rats have been reported to occur spontaneously and secondary to chemical induction (13,18,26,37,35). The histologic hallmarks of these lesions are neoplastic chondrocytes and surrounding cartilaginous matrix. Osteoid and/or bone may occur in cartilaginous neoplasms through metaplastic transformation of non-neoplastic fibroblastic mesenchymal cells and endochondral ossification.

Chordomas are rare neoplasms derived from vestigial remnants of the embryonal notochord. They are classified along with cartilaginous lesions, because of the morphologic and functional similarities of notochord and cartilage. Benign and malignant chordomas have been reported in rats (17,18,21,28,29,39,43,46). They originate along the axial skeleton, primarily in the lumbosacral region, but have also been reported at the base of the skull. Local tissue invasion and destruction and pulmonary metastases are common with malignant chordomas.

## MORPHOLOGY

### ***CARTILAGE HYPERPLASIA (Figure 19)***

Cartilage hyperplasia is recognized by the presence of an increased amount of well-differentiated, but irregularly arranged, cartilage and/or chondrocytes. Growth may appear expansive but not infiltrative. Chondrocytes often occur in clusters within more closely arranged lacunae. The matrix generally stains lightly basophilic with H&E, but may stain pink (chondroid) if depleted of proteoglycans. Cartilage hyperplasia commonly occurs in association with trauma, inflammation, or mucinous degeneration.

### ***CHONDROMA (Figure 20)***

Chondromas are expansile, circumscribed masses composed of irregular lobules of cartilage. Chondrocytes lack orderly arrangement, but are well-differentiated and generally arranged individually within lacunae. Individual chondrocytes exhibit minimal cellular and nuclear pleomorphism and mitotic figures are very rare. As in normal cartilage, occasional bicellular lacunae may be seen, but multinucleated chondrocytes are absent. The surrounding matrix is amorphous and lightly basophilic. Chondromas do not metastasize or invade surrounding tissues. Areas of osseous metaplasia and/or chondroid formation may occur within chondromas and should not be confused with bone matrix production by neoplastic osteoblasts. Chondromas have been reported to occur in the nasal turbinates of rats (18).

### ***CHONDROSARCOMA (Figures 21,22)***

Chondrosarcomas are derived from chondroblasts or pluripotential mesenchymal cells that undergo malignant transformation. They are often hypercellular, but maintain characteristic areas of differentiated chondrocytes surrounded by a cartilaginous or mucinous matrix. Cells lack orderly arrangement and their nuclei may exhibit pleomorphism with multiple nuclei per lacuna. Mitoses are generally rare. Less differentiated areas composed of spindled or vacuolated cells may be seen. Local tissue infiltration may occur, and pulmonary metastases are common. As in chondromas, osteoid and/or bone may occur in chondrosarcomas through metaplastic transformation of non-neoplastic fibroblastic mesenchyme or through stimulation of non-neoplastic periosteal cells (24). In rats, chondrosarcomas have been reported to occur spontane-

ously (13,18,35) and secondary to chemical induction (26,37). Because chondrosarcomas in rats are often well-differentiated, their distinction from chondromas may be difficult and involve critical assessment of cellular pleomorphism and histologic evidence of invasion or metastases.

### ***CHORDOMA (Figure 23)***

Chordomas are rare neoplasms of older rats that arise from remnants of the embryonic notochord (36,28). They occur along the spinal cord, primarily in the lumbosacral region, and are composed of large, polygonal to round, vacuolated (physaliphorous) cells arranged in irregular lobules separated by fibrous connective tissue bands. The cytoplasmic vacuoles are variably-sized and unstained by hematoxylin and eosin. The round to oval nuclei are centrally to eccentrically located, small to medium-sized, and contain a small, but distinct, nucleolus. Mitoses are rare. Smaller, stellate cells are sometimes present, and believed to be precursors to the physaliphorous cells. A mucinous ground substance may be deposited around some of the less vacuolated and stellate cells. Benign chordomas are well-circumscribed and show no evidence of tissue infiltration.

### ***MALIGNANT CHORDOMA (Figure 24)***

The majority of chordomas in rats are considered malignant (18,29,39). They exhibit extensive tissue infiltration and destruction of adjacent bone and soft tissues. Pulmonary metastases are common. Microscopically, malignant chordomas are composed of irregular sheets and lobules of physaliphorous or stellate cells, and are differentiated from benign chordomas by their metastases and infiltration of local tissues. Areas of necrosis are common within larger lobules and bands of neoplastic tissue. The incidence of malignant chordomas in rats is higher in males than females (39), which is also true of chordomas in man (16).

Chordomas must be differentiated from liposarcomas and cartilaginous neoplasms. They can be distinguished by histochemistry and immunohistochemistry. Chordomas are lipid-negative (oil-red-O, Sudan IV), periodic acid-Schiff (PAS)-positive, keratin-positive, vimentin positive, neuron-specific enolase-positive, and S100 protein-positive. Liposarcomas are lipid-positive and PAS-negative. Chondromas and chondrosarcomas are negative for keratin.

## DISCUSSION

In man, cartilaginous tumors are sub-classified according to morphology, site of occurrence, clinical expression, and histologic grade of differentiation for therapeutic and prognostic purposes (36). In toxicologic pathology, such subclassification is not generally required because the study objectives are not therapeutically and/or prognostically driven. The simple classification of proliferative cartilaginous lesions proposed here for rats, however, doesn't translate to an easy diagnosis. The pathologist must carefully examine the tissue to derive a diagnosis of cartilaginous neoplasia and potential malignancy. Cartilaginous differentiation may occur in other mesenchymal neoplasms, such as osteosarcomas and fibrosarcomas, but should not necessarily confer a diagnosis of a cartilaginous neoplasm. The pathologist's evaluation of the matrix produced by the tumor cells and the predominant cytologic differentiation should influence the final diagnosis. The production of osteoid by malignant stromal cells, however, is diagnostic of an osteosarcoma, even if the tumor appears primarily cartilaginous. Cartilaginous metaplasia may also occur in non-proliferative lesions such as sites of extensive fibrosis (scarring).

## TOOTH

### INTRODUCTION

In normal tooth development, the ameloblastic epithelium exerts an influence upon the undifferentiated mesenchymal cells of the pulp, causing the adjacent cells to differentiate into odontoblasts (12). The odontoblasts then proceed to deposit dentin. The formation of dentin in turn has a reciprocal inductive effect upon the ameloblasts, causing them to deposit enamel. This is the normal sequence of events that has been used as a basis for the classification of tooth tumors in man and animals (12). The epithelial tumors are subdivided according to the presence or absence of an inductive change in the adjacent connective tissue. Each of these classes is further divided according to the type of stroma and the presence of hard or soft dental tissue (12).

The incisor teeth of rats grow throughout life (7,33). On the convex side, the dentin is covered by a layer of enamel and the enamel organ. A film of iron is deposited between the dentin and enamel, giving rat incisors a yellow appearance. On the concave side of the incisor the dentin is enamel-free, but has a very thin layer of cementum into which the fibers of the periodontal ligament are embedded.

Tooth tumors reported in the rat include

ameloblastoma (19,34), ameloblastic odontoma (1,8,10,34,40), and both complex and compound odontoma, (7,30,34). Spontaneous tooth tumors are very rare in rats, with too few published reports to make any generalizations about their behavior or preferential sites of development (1,10). The vast majority of induced proliferative lesions of rat teeth occur in the incisors (5,7,34). "Odontome-like" formations have been reported in a mutant strain of rat (33).

## MORPHOLOGY

### AMELOBLASTOMA

Ameloblastomas are epithelial neoplasms that do not form enamel, dentin, or cementum (12). They appear to arise from several possible origins: the epithelial lining of a dentigerous cyst; the remnants of the dental lamina and of the enamel organ; and the basal layer of the oral mucus membrane. Most ameloblastomas will demonstrate either a follicular or plexiform growth pattern. In the follicular form, epithelial cells are arranged in islands mimicking the enamel organ in which the outer most cells are tall columnar (resembling those of the inner enamel epithelium) and the central epithelial cells are more loosely arranged and resemble the stellate reticulum seen in normal tooth germ. The plexiform pattern demonstrates irregular masses and interdigitating cords of epithelial cells with a variable amount of stroma. The area corresponding to the stellate reticulum is less well defined than in the follicular type; however, the border cells are clearly ameloblastic in nature.

### AMELOBLASTIC ODONTOMA (*odontoameloblastoma*) (Figure 25)

Ameloblastic odontomas are dental neoplasms composed of a soft tissue component resembling ameloblastoma and a hard tissue component (dentin, enamel, and/or cementum) resembling odontoma (12,34). The histologic features of ameloblastic odontoma are variable, but the soft tissue component (resembling ameloblastoma) is generally located at the periphery of the mass and the hard tissue component (resembling complex or compound odontoma) is usually centrally located. The ameloblastic component tends to behave aggressively.

### **ODONTOMA (Figure 26)**

The term "odontoma" refers to a dental neoplasm (or hamartoma) in which maturation has progressed to the stage of development of both enamel and dentin (12). Two types are recognized in rats: complex odontoma and compound odontoma. The complex and compound odontoma differs from the ameloblastic odontoma by the absence of distinct areas of ameloblastic tissue that lack hard tissue elements. Complex odontomas contain dental pulp mesenchymal cells and hard tissue elements, but there is very poor morphodifferentiation, resulting in a mass that has little resemblance to normal tooth architecture. In contrast, the compound odontoma exhibits a high degree of morphodifferentiation, and the hard tissue elements actually resemble small deformed teeth. The hard tissue generally appears as dentin (an acellular, smooth, eosinophilic material) with smaller amounts of cementum (resembling bone). Enamel may be completely removed upon decalcification (since it is 95% mineral), in which case it will appear as a clear space or cleft in close apposition to the dentin. Incompletely decalcified specimens may have a small amount of enamel that stains basophilic with hematoxylin and eosin.

### **DISCUSSION**

Non-neoplastic proliferative alterations involving teeth are poorly documented in rats; however, they do occur. Most of these non-neoplastic proliferative tooth lesions involve incisor teeth that have been fractured during trimming for treatment of malocclusion. Infection and attempted repair may result in atypical hyperostotic lesions involving cementum, odontoblasts, and displaced ameloblasts.

## **SYNOVIUM**

### **INTRODUCTION**

The synovium consists of 1-3 layers of squamoid to cuboidal epithelial cells (synoviocytes), supported by a fatty and fibrovascular stroma (18,44). Larger accumulations of subsynovial adipose tissue ("fat pads") are found in some joints (notably the stifle) and may project into the joint space. Small villous projections of the synovial membrane are normally present in the niches of joints. Less-differentiated synovioblastic cells are also present and are thought to be the precursors of neoplasms (4,15).

In addition, the transitional zone, where the synovium merges with the periosteum or perichondrium, is thought to be the site of pannus and osteophyte formation, and villus hyperplasia (15). The proliferative ability of the synovium is high, probably related to its highly vascular nature (15).

### **MORPHOLOGY**

#### **SYNOVIAL HYPERPLASIA (Figure 27)**

Synovial hyperplasia in the rat is characterized by both hypertrophy of the synovium and hyperplasia of the synoviocytes (18). The synovial lining cells become clearly stratified and cuboidal, and may produce papillary projections into the joint lumen; they may become oriented perpendicular to the synovial membrane (3). Synovial hyperplasia is often accompanied by inflammatory or degenerative changes, such as: mononuclear inflammatory cell infiltration of the synovium; granulation tissue formation (pannus); increased subsynovial vascularity; hemosiderin containing macrophages; or degenerative lesions of the adjacent cartilage and bone.

#### **SYNOVIAL SARCOMA (Figure 28)**

Synovial sarcomas may arise along tendon sheaths, bursae, and joints. Because of their villous nature, they may appear "velvety" or "shaggy" grossly. Microscopically, synovial sarcomas may have a biphasic pattern with epithelioid and fibrosarcomatous components (6,11). The fibrosarcomatous component consists of small, plump, spindle-shaped cells densely grouped in bands or sheets. The epithelioid component consisted of dense populations of plump ovoid or polyhedral cells separated by irregular spaces and clefts with frequent branching. Growth is locally destructive and invasion into the adjacent bone is common. Multinucleated giant cells are occasionally observed. The mitotic rate is usually low.

### **DISCUSSION**

Spontaneous synovial sarcomas occur infrequently in rats (18) and there are only a few reports of induced synovial sarcomas in rats (6,11). The biphasic pattern reported in rat synovial sarcomas is similar to that described for human synovial sarcomas. Benign synoviomas are not known to occur in the rat.

## NOMENCLATURE AND DIAGNOSTIC CRITERIA

### BONE

#### *HYPEROSTOSIS*

1. Increased skeletal bone mass.
2. Occurs in close proximity to pre-existing bone surfaces.
3. Growth may be expansile but not infiltrative.
4. Bone trabeculae are woven or lamellar and tend to form organized "looping" or "networking" pattern.
5. Stromal cells do not exhibit anaplasia.
6. Intertrabecular stroma is generally hypocellular but vascular.
7. May see osteoblast "rimming" of bone trabeculae.
8. May have areas of cartilage formation, inflammation, fibroplasia, and giant cells.

#### *CALLUS*

1. Hyperostosis in repair of a bone fracture.
2. Contains osteoid, bone, cartilage, in all forms of maturity; osteoclast-like giant cells; or spindly fibroblast-like tissues in all forms of maturity.
3. Zonation phenomenon in reverse of osteosarcoma (matrix production begins at periphery and spreads toward more "immature" center).
4. Osteoblast rimming of bone trabeculae.
5. May see woven bone core cuffed by lamellar bone.
6. May trap host lamellar bone.
7. Histology is influenced by mechanical stability and time.

#### *OSTEOPHYTE*

1. Expansile periarticular hyperostotic mass.
2. Accompanied by degenerative joint disease and/or displacement of the perichondrial ring.
3. Immature forms may be extensively cartilaginous.
4. Mature forms consist of lamellar bone and a core of marrow with or without a cartilage cap.

#### *FIBRO- AND CHONDRO-OSSEOUS METAPLASIA*

1. Transformation of fully differentiated fibroblastic tissue into non-neoplastic bone and/or cartilage.
2. Occurs in soft tissues, hyperostoses, and osseous and non-osseous tumors.
3. The bone and/or cartilage is partly bordered by fibroblastic tissue.
4. Bone is formed with or without a cartilage template.

#### *OSTEOCHONDROMA*

1. Expansile cartilage-capped osseous mass arising from the external bone surface.
2. Outer rim of cartilage has growth plate-like appearance.
3. Endochondral ossification along inner margin of cartilage.
4. Tumor core contains lamellar bone trabeculae and abundant marrow.
5. Tumor core may be seen to communicate with marrow of parent bone.
6. Not associated with degenerative joint disease or displacement of perichondrial ring.

#### *OSTEOMA*

1. Expansile bone mass with well-defined outer margins.
2. Preferentially arise from the periosteal surface.
3. Composed of dense bone core (predominantly lamellar) with few cells.
4. May see active or inactive osteoblasts along outer trabeculae.
5. Base of tumor blends with underlying cortical bone.
6. Intertrabecular spaces may contain marrow elements.

#### *OSTEOSARCOMA*

1. Tumor cells produce osteoid and generally exhibit high-grade anaplasia.
2. Invasive and destructive growth or metastasis.
3. Frequent mitotic figures.
4. Zonation with most "immature" (non-productive) cells at periphery.
5. Cells may form "permeative" pattern at the lesion host-bone interface, "entrapping" host lamellar bone.
6. Variable features include cartilage, fibroblastic tissue, large blood-filled spaces, osteoclast-like giant cells, periosteal hyperostosis, and necrosis.
7. Tumor cells do not produce lamellar bone or form osteoblast "rimming" sign.
8. Organized interconnected "looping" of tumor bone is absent.

## CARTILAGE

#### *CARTILAGE HYPERPLASIA*

1. Increased amount of well-differentiated cartilage and/or chondrocytes, often with chondrocytes arranged in clusters within lacunae.
2. Usually focal and associated with tissue trauma, inflammation, or mucinous degeneration.
3. Matrix may be chondroid in appearance.
4. Growth may appear expansile.
5. No evidence of local tissue infiltration.

**CHONDROMA**

1. Circumscribed expansile mass composed of irregular lobules of mature cartilage.
2. Cells lack orderly arrangement, but are well-differentiated and generally arranged individually within lacunae.
3. Matrix usually stains lightly basophilic but may be partly chondroid in appearance.
4. Osseous metaplasia may be present.
5. No cellular/nuclear pleomorphism, local infiltration, or metastases.

**CHONDROSARCOMA**

1. Solid, irregularly lobulated, non-encapsulated mass composed of chondrocytes surrounded by cartilaginous or mucinous matrix.
2. Disorganized/infiltrative growth pattern or metastasis.
3. Hypercellular areas with cellular pleomorphism and multiple nuclei per lacunae.
4. Less differentiated areas of spindled or vacuolated cells.
5. Rare mitoses.
6. Neoplastic cells do not directly produce osteoid or bone, but endochondral ossification and/or osseous metaplasia of trapped mesenchyme may occur.

**CHORDOMA**

1. Encapsulated mass of large vacuolated (physaliphorous) cells arranged in lobules separated by bands of fibrous connective tissue.
2. Located along the spinal column, usually lumbosacral.
3. Cells are arranged in solid sheets and have distinct cytoplasmic borders, single or multiple cytoplasmic vacuoles, and round to oval nuclei that are centrally or eccentrically located.
4. "Signet-ring cells" with peripherally located nuclei, cells with homogeneous or granulated cytoplasm, and smaller stellate cells may also be present.
5. Mucin production may be observed using special stains.
6. Mitoses are rare.

**MALIGNANT CHORDOMA**

1. Cellular morphology similar to benign chordoma.
2. Infiltration and destruction of adjacent tissues or metastasis.

**TOOTH****AMELOBLASTOMA**

1. Expansile mass involving a tooth.
2. Composed of epithelial cells arranged in islands (follicular type) or interdigitating cords (plexiform

type) mimicking the enamel organ.

3. Outer most cells are tall columnar (resembling the inner enamel epithelium).
4. Central epithelial cells are loosely arranged (resembling stellate reticulum).
5. Do not form hard tissues (enamel, dentin, or cementum).

**AMELOBLASTIC ODONTOMA  
(ODONTOAMELOBLASTOMA)**

1. Expansile mass involving a tooth.
2. Consists of a soft tissue component (resembling ameloblastoma) and a hard tissue component (resembling complex or compound odontoma).
3. The soft tissue component (resembling ameloblastoma) is generally located at the periphery of the mass.
4. The hard tissue component (resembling complex or compound odontoma) is usually centrally located.
5. The ameloblastic component tends to behave aggressively.

**ODONTOMA**

1. Expansile mass involving a tooth.
2. Complex odontoma contains most tooth components (cementum, dentin, enamel, and dental pulp mesenchymal cells) but there is poor morphodifferentiation and little resemblance to of normal tooth structure.
3. Compound odontoma contains the same elements as the complex form and there is a high degree of morphodifferentiation with formation of structures that resemble small deformed teeth.

**SYNOVIUM****SYNOVIAL HYPERPLASIA**

1. Increased number of relatively uniform and well differentiated synoviocytes.
2. Synoviocytes and underlying stroma maintain organized appearance.
3. Usually associated with inflammatory or degenerative joint disease.

**SYNOVIAL SARCOMA**

1. Located near tendon sheaths, bursae, and joints.
2. Locally invasive and destructive.
3. Appear as loosely organized fronds or villous projections composed of a dense population of small, cuboidal epithelioid cells, with indistinct cell borders.
4. Multinucleated giant cells are occasionally observed.
5. May be biphasic with epithelial and mesenchymal components intimately admixed.

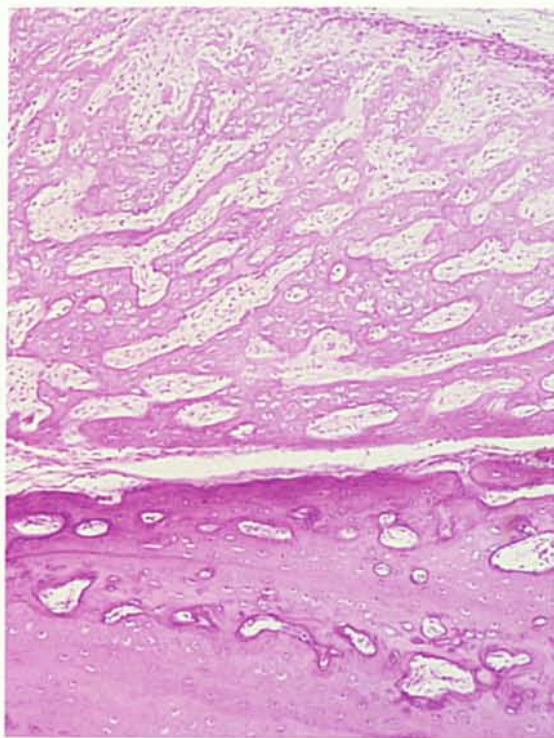
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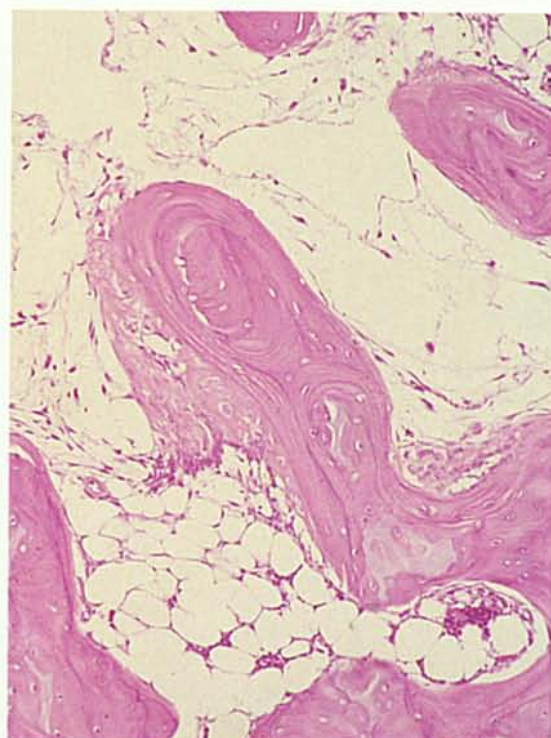
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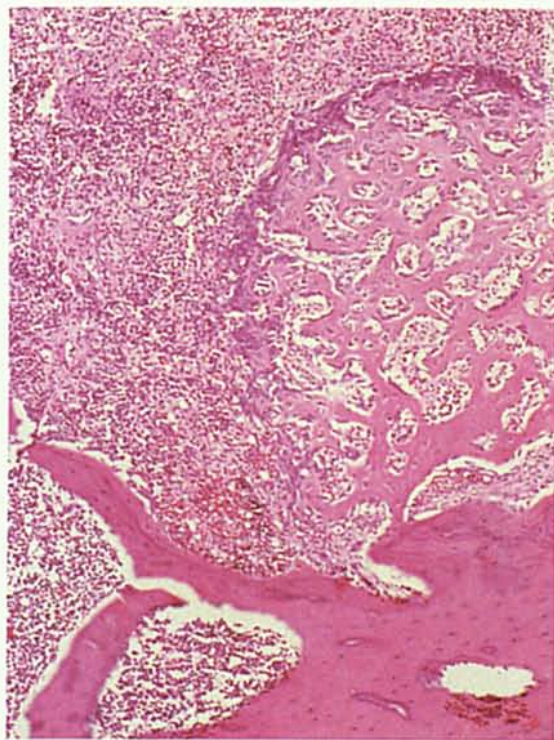
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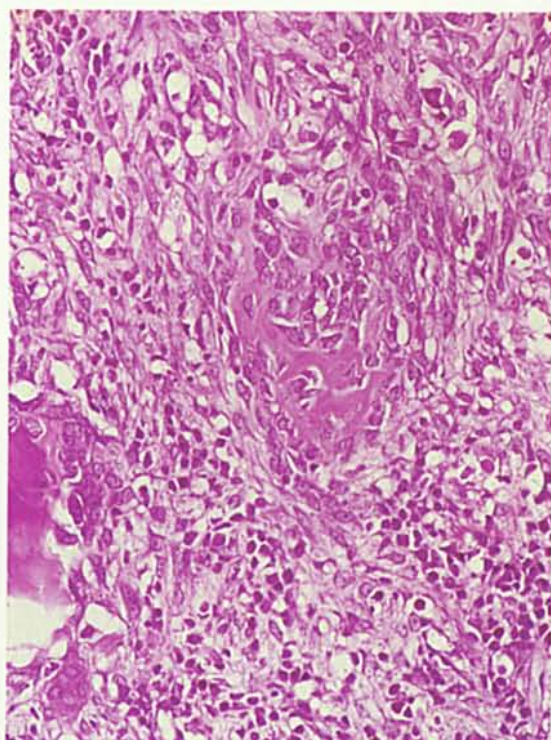
**Fig.1.** Hyperostosis, periosteal - Expansile mass of woven bone with organized "networking" (looping) of bone trabeculae (H&E, 37.5x).



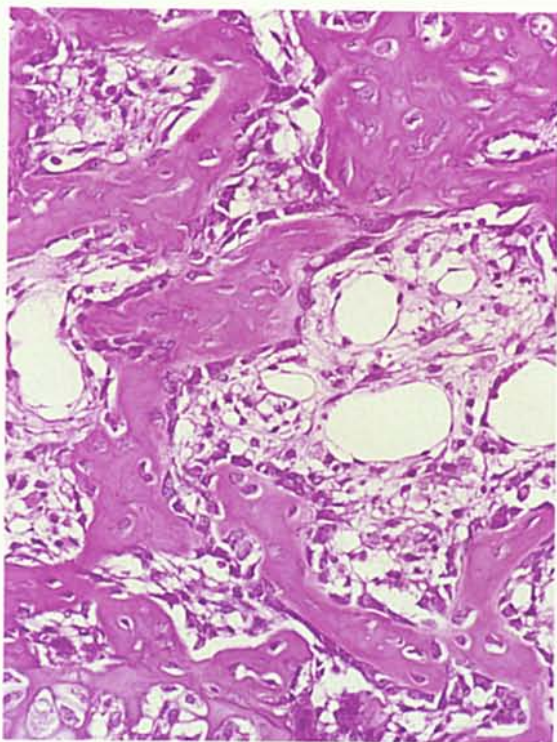
**Fig. 2.** Hyperostosis, peritrabecular - Increased bone formation along bone trabeculus (H&E, 150x).



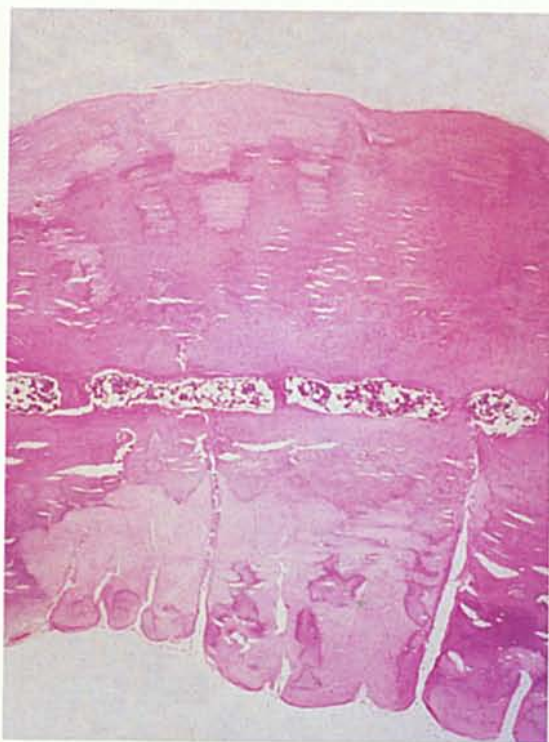
**Fig. 3.** Hyperostosis, endosteal, focal - Expansile bone mass along endosteum secondary to osteomyelitis. Note networking of trabeculae and osteoblast rimming of bone (H&E, 37.5x).



**Fig. 4.** Hyperostosis, medullary, focal - Bone formation following adjuvant-induced arthritis. This field appears atypical due to an absence of trabecular networking and a lack of organized osteoblast rimming. (H&E, 187.5x).



**Fig. 5.** Hyperostosis, medullary, focal - Adjacent field from same rat as in Fig. 4. Note clear-cut osteoblast rimming, early trabecular networking, hypocellular intertrabecular stroma, and prominent capillaries (H&E, 187.5x).



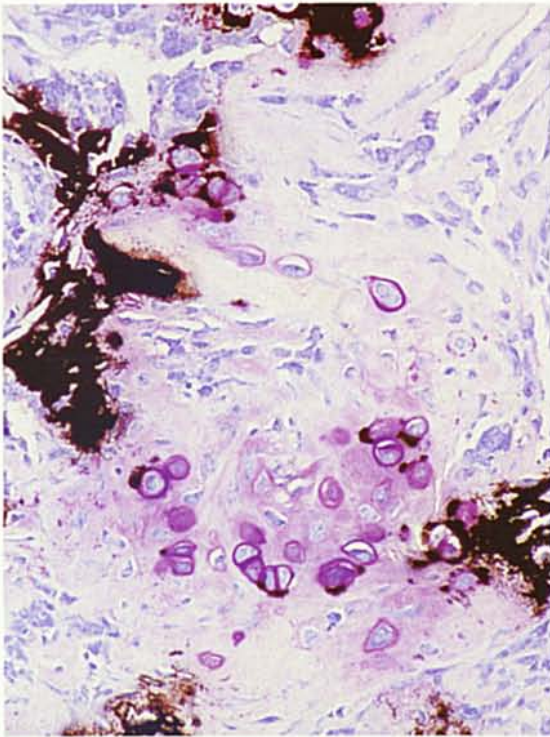
**Fig. 6.** Hyperostosis, subperiosteal, diffuse - Thickened calvarium following chronic exposure to sodium fluoride. Note mature lamellar bone with lakes of osteoid and an absence of osteoblast proliferation. (H&E, 18.6x).



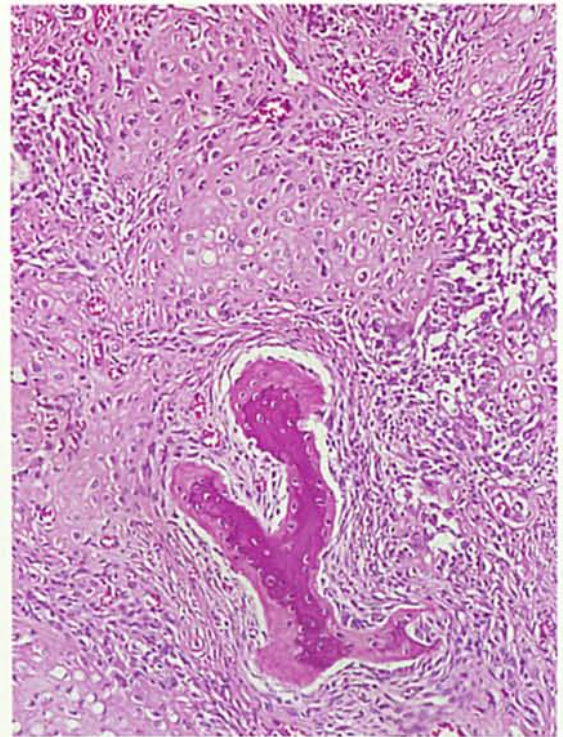
**Fig. 7.** Callus - Fractured bone cuffed with cartilage undergoing endochondral ossification (H&E, 37.5x).



**Fig. 8.** Osteophyte, perivertebral, multiple - Expansile bone/cartilage masses along the ventral margins of intervertebral disc spaces (H&E, 9x).



**Fig. 9 – Chondro-osseous metaplasia** - Cartilage and bone formation from non-osseous fibroblastic tissue that was induced by a bone morphogenic protein (von Kossa-Toluidine Blue, 234x).



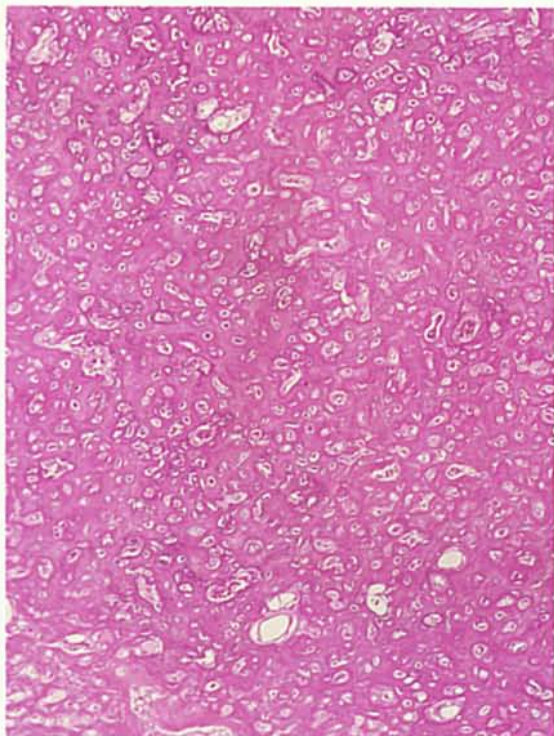
**Fig. 10. Fibro-osseous metaplasia** - Bone formation from non-osseous fibroblastic tissue secondary to inflammation of the ear. Also, note chondroid appearance of hyperplastic cartilage (H&E, 93.6x).



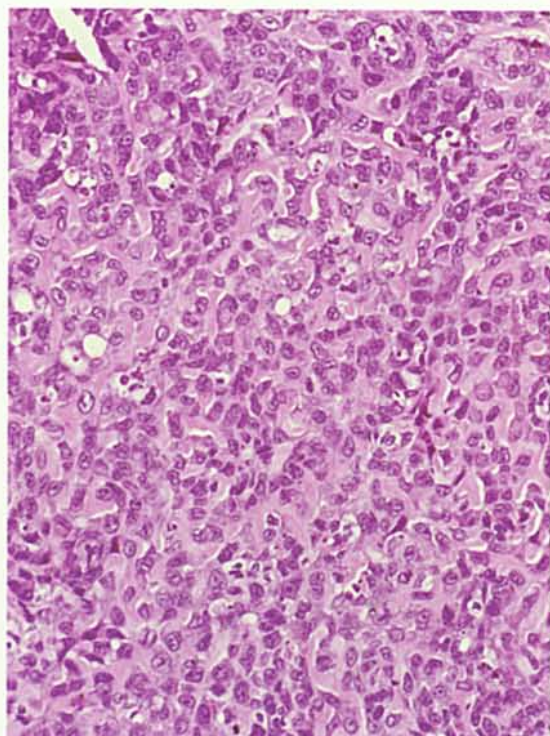
**Fig. 11. Osteochondroma** - Expansile mass with outer rim of proliferating growth plate-like cartilage and a bone marrow-like core (H&E, 9x).



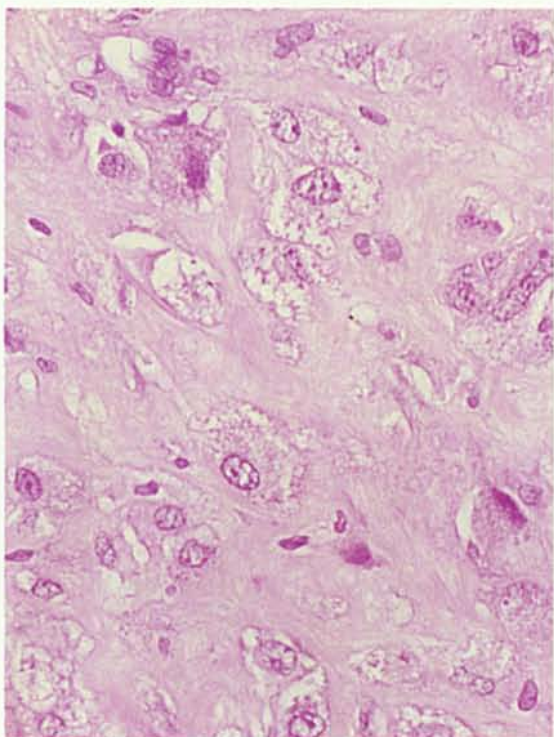
**Fig. 12. Osteoma** - Expansile mass with dense inner trabecular framework (H&E, 9x).



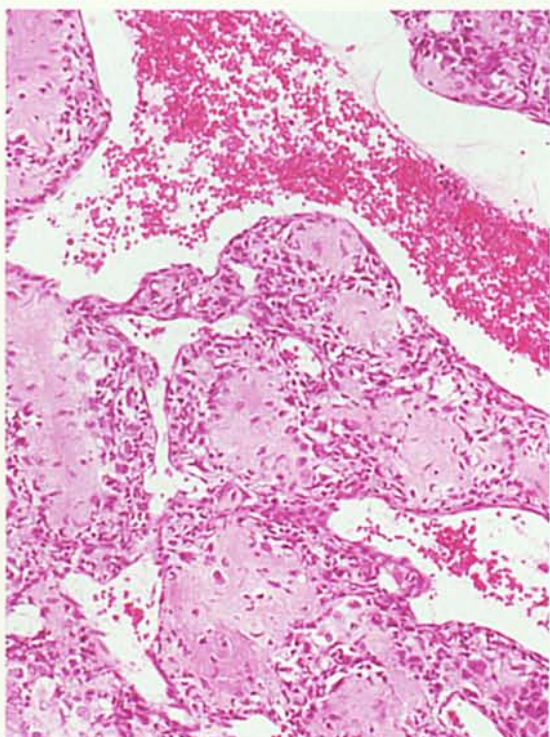
**Fig. 13.** Osteoma - Higher magnification of Figure 12 (H&E, 37.5x).



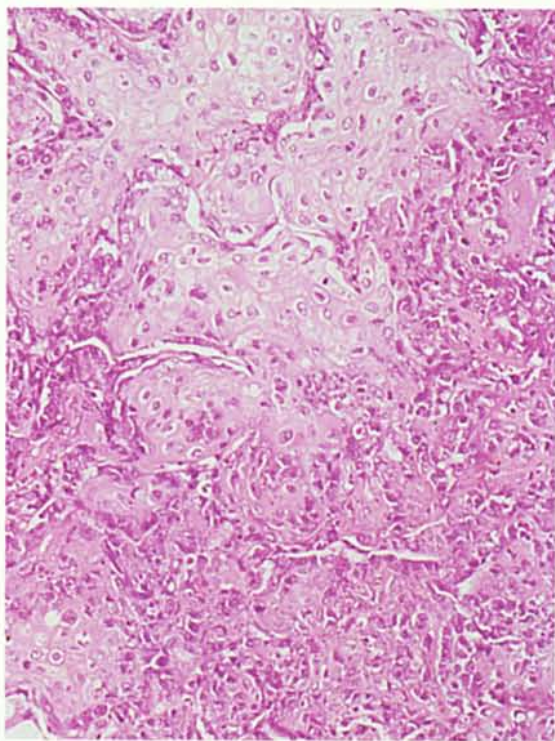
**Fig. 14.** Osteosarcoma - Osteoblastic type with small islands of osteoid separated by a dense population of pleomorphic osteoblasts (H&E, 187.5x).



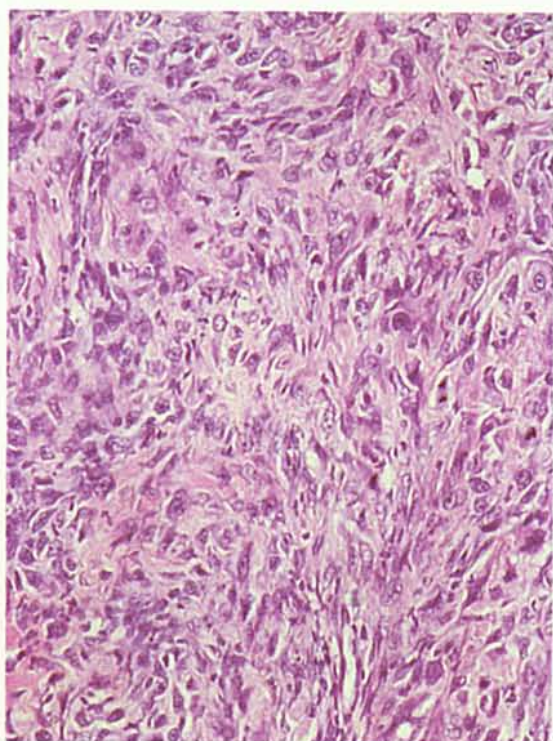
**Fig. 15.** Osteosarcoma - Osteoplastic type with large amounts of osteoid and scattered pleomorphic osteoblasts (H&E, 375x).



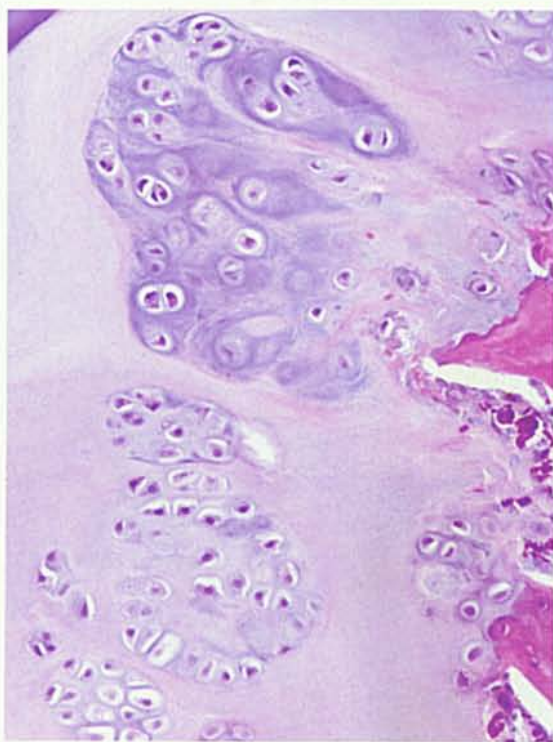
**Fig. 16.** Osteosarcoma - Telangiectatic type with large blood-filled spaces, islands of osteoid, and moderate numbers of pleomorphic osteoblasts (H&E, 93.6x).



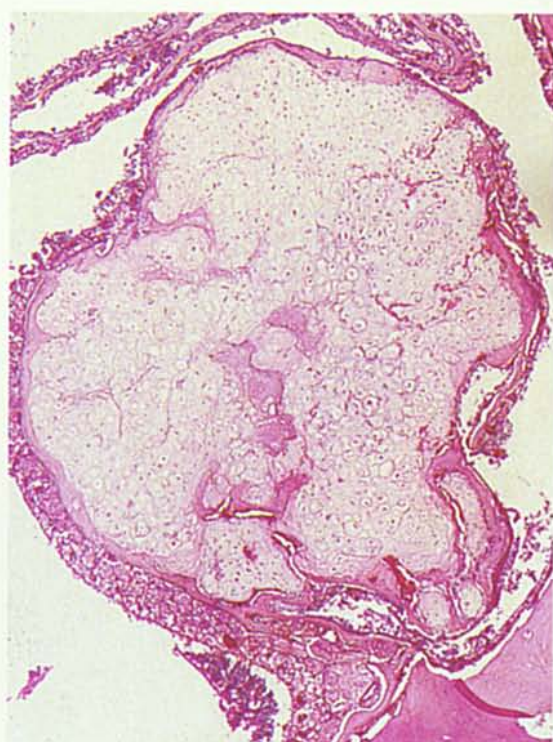
**Fig. 17.** Osteosarcoma - Compound type with islands of neoplastic cartilage (H&E, 93.6x).



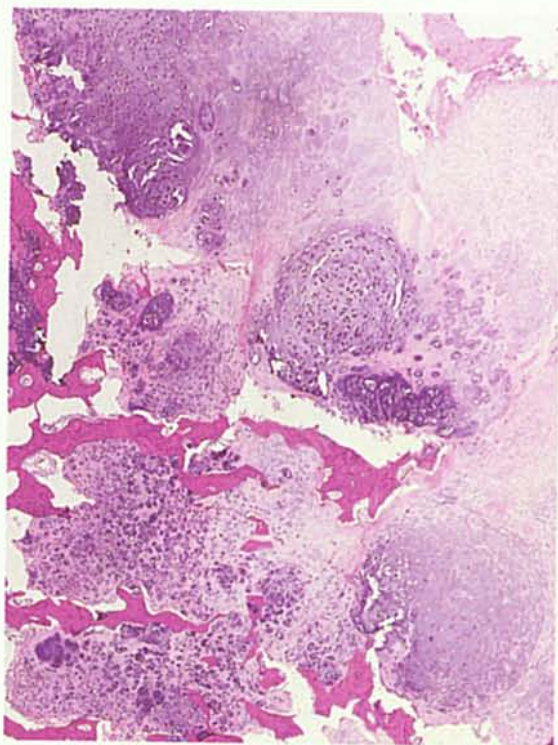
**Fig. 18.** Osteosarcoma - Fibroblastic type with spindle-shaped cells and a small island of osteoid (H&E, 187.5x).



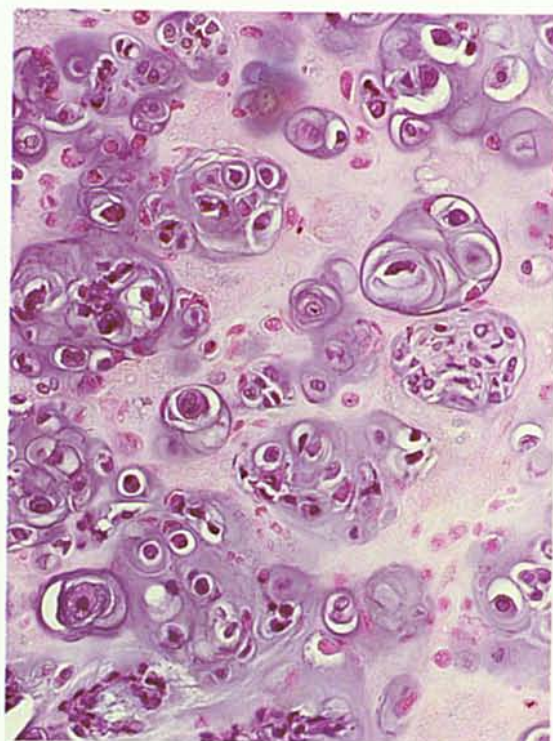
**Fig. 19.** Cartilage Hyperplasia - Increased numbers of well-differentiated chondrocytes arranged in clusters within lacunae (H&E, 187.5x).



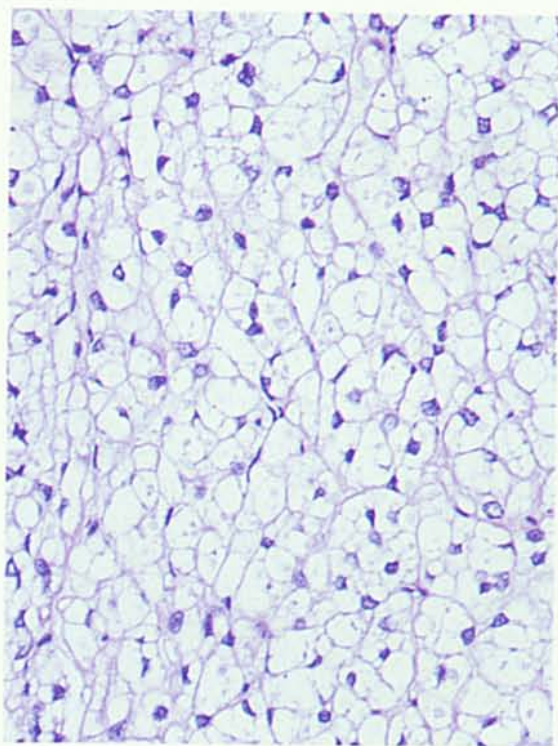
**Fig. 20.** Chondroma (nasal cavity) - Circumscribed mass of disorganized cartilage consisting of well-differentiated chondrocytes separated by lightly basophilic matrix. Note area of osseous metaplasia in center of mass (H&E, 37.5x).



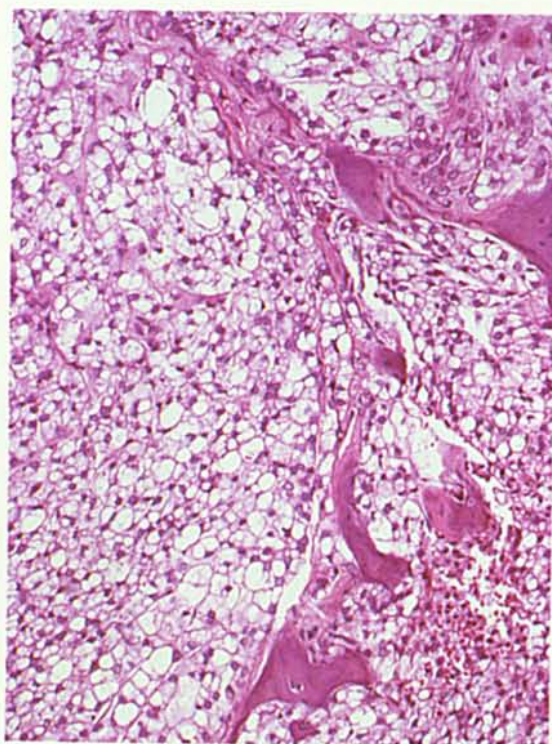
**Fig. 21.** Chondrosarcoma - Disorganized mass of pleomorphic chondrocytes with infiltration (permeation) of normal bone (H&E, 9x).



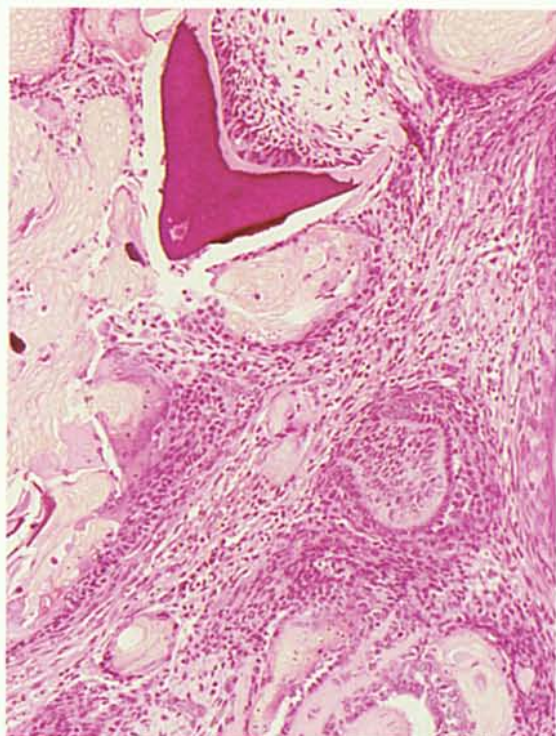
**Fig. 22.** Chondrosarcoma - Higher magnification of Figure 21 (H&E, 375x).



**Fig. 23.** Chordoma - Sheets of characteristic physaliphorous (vacuolated) cells (H&E, 150x).



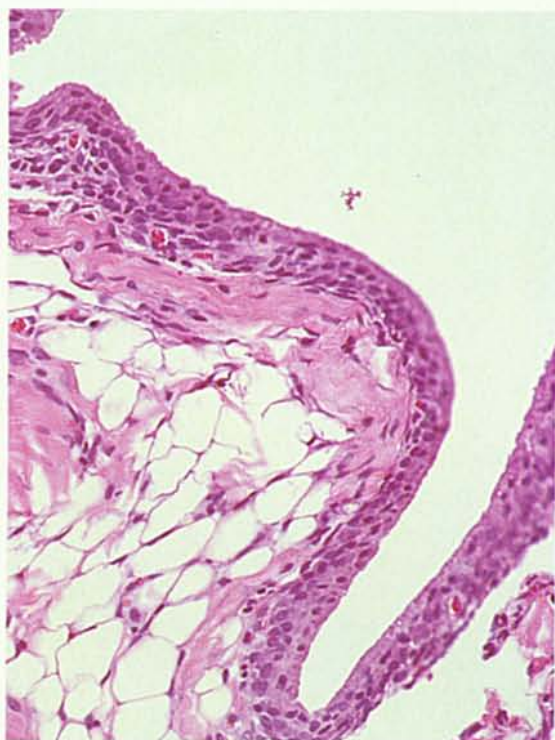
**Fig. 24.** Malignant Chordoma - Sheets of characteristic physaliphorous (vacuolated) cells infiltrating normal lamellar bone (H&E, 93.6x).



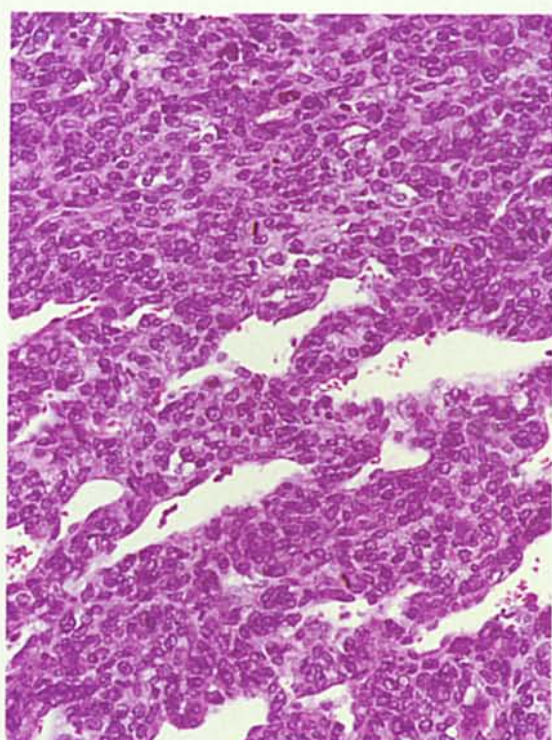
**Fig. 25.** Ameloblastic odontoma - Proliferation of ameloblastic odontogenic epithelium in combination with haphazardly arranged dental hard tissue elements (H&E, 93.6x).



**Fig. 26.** Odontoma - Complex type consisting of a disorganized mass of dental hard tissue elements separated by pulp-like mesenchymal cells (H&E, 37.5x).



**Fig. 27.** Synovial hyperplasia - Increased numbers of well-differentiated synoviocytes arranged in multiple stratifications (H&E, 150x).



**Fig. 28.** Synovial sarcoma - Disorganized densely cellular mass of atypical epithelioid cells arranged in sheets separated by cleft-like spaces (H&E, 187.5x).