Pyrophosphate Arthropathy, *Macaca mulatta*

E. Donald Roberts

**Synonyms.** Pseudogout; calcium pyrophosphate deposition disease; chondrocalcinosis.

**Gross Appearance**

Pseudogout is a disease of the joints and intervertebral disc and is associated with chronic degenerative joint disease of primarily the knee articular cartilage and menisci. Cartilage changes are characterized by marginal erosion of cartilage, ulceration, fibrillation of articular cartilage and osteophyte formation (Fig. 149). The chronic knee joint changes are also associated with muscle and tendon contraction, which prevents the extension of the knee joint. If sufficient quantity of the pyrophosphate crystals are present, a focal whitish discoloration of the cartilage or menisci will be evident (Fig. 149). Radiographically, focal radiodensities may be observed in the affected tissues (Kessler et al. 1986).

**Microscopic Appearance**

Joint changes are usually accompanied by an acute inflammatory reaction of the synovium consisting of numerous neutrophils, fibrin and lymphoid infiltrate (Fig. 150). Focal bluish granular accumulations are present in the cartilage matrix, many of which appear to originate in the germinal zone of the cartilage. The crystal deposition is usually accompanied by reduced cartilage cellularity and cloning of the chondrocytes with fibrillation of the frictional surface of the cartilage. Degenerating hypertrophic chondrocytes are associated with crystal formation (Ishikawa et al. 1989). Using polarized light microscopy, rhomboid-shaped structures are strongly birefringent.

**Ultrastructure**

Scanning electron microscopy is a good diagnostic tool, as the pyrophosphate crystals have a characteristic rhomboid morphology and tend to form clusters emanating from the articular cartilage (Fig. 151). The crystals tend to be layered and slate-like. Identification of the crystals by elemental analysis and/or diffraction is essential for a definitive diagnosis (Fig. 152). Crystals are usually present within the joint and embedded into the lining synovial cell layer (Fig. 153).

**Differential Diagnosis**

Most crystal arthropathies are associated with chronic joint diseases. The acute flare-up is associated with crystals that are free within the joint. The initial diagnostic phase should include demon-
stratification of crystals by compensated polarized light microscopy. With use of a first order lambda compensator, one can distinguish between urate and pyrophosphate crystals. Since gout is not a problem in nonhuman primates, polarized light microscopy identification of birefringent crystals is very significant. The next level of evaluation should include scanning electron microscopy combined with elemental analysis. The concentration of calcium and phosphate ions should be approximately equal. Crystals to be distinguished should include brushite, an intermediate form of apatite (CaHPO$_4$*2H$_2$O); hydroxyapatite (Ca$_5$OH(PO$_4$)$_3$*H$_2$O); and pyrophosphate (Ca$_3$P$_2$O$_7$*2H$_2$O).

**Biologic Features**

Pyrophosphate arthropathy is a degenerative arthritis characterized by the deposition of calcium pyrophosphate dihydrate crystals in articular cartilage menisci and intervertebral disc (Resnick and Resnick 1983). The condition was first recognized in humans by McCarty in 1962. The pathogenesis of the disease is poorly understood; however, it is apparent that the disease is related to increasing age and/or degenerative changes of hyaline cartilage (Roughley and White 1980; Roughley and White 1980; Roberts et al. 1984b; Kessler et al. 1986) in both humans and rhesus monkeys. Altered metabolism of hypertrophic chondrocytes is associated with crystal formation (Tennenbaum et al. 1981; Ishikawa et al. 1989). Collagen fibrils undergoing degradation promote crystallization by nucleation (Mandel et al. 1984; Pritzker et al. 1978). Normally chondroitin sulfate inhibits the formation of pyrophosphate crystal deposition by binding calcium ions and by stabilization of intermediate calcium magnesium pyrophosphate (Hunter 1987). Thus any arthropathy that promotes the release of mediators of inflammation may trigger the release or production of chondrocyte neutral proteases, setting the stage for pyrophosphate crystal formation. That pyrophosphate crystals are the causal agent in acute pseudogout has been demonstrated both in vitro and by the injection of pyrophosphate crystals into normal human joints where an acute arthropathy was produced (McCarty 1963). The crystals shed within the joint are chemotactic (McCarty and Kozin 1975), thus initiating the inflammatory process within the joint (Bennett et al. 1976; Kohn et al. 1962).

![Fig. 149. Macaca mulatta. Chronic degenerative joint disease with multifocal areas of ulceration and erosion of cartilage (E). Note the focal, white, granular material representing calcium pyrophosphate crystal deposition (arrowhead)](image)

**Comparison with Other Species**

The disease in nonhuman primates reported in rhesus monkeys (*Macaca mulatta*) and one Barbary ape (*Macaca sylvana*), (Kandel et al. 1983; Roberts et al. 1984a,b; Renlund et al. 1986; Kessler et al. 1986) parallels the disease observed in humans. Both occur in older individuals, are associated with degenerative joint disease and affect the same range of connective tissue structures. The nonhuman primate disease represents a naturally occurring model of the disease of humans. Articular mineralization has been reported from various species. Subcutaneous, white granulomat-