Introduction - Osteoarthritis (OA) is a leading cause of disability in the world. One approach to the study of the disease has been through animal models. "Quick models" are used to answer disease-specific questions and study surrogate markers of joint disease, but may not manifest all aspects of the disease process. Actual disease models include mechanical destabilization of the joint or animal models in which OA is a spontaneously occurring disease. Male Hartley albino guinea pigs have been reported to develop focal lesions on the medial tibial plateau as early as 3 months of age\textsuperscript{1-3}. Little is known about degenerative changes in other joints or matrix changes that precede histologic evidence of lesions. The purpose of this study was to evaluate extracellular matrix changes in the knee joint cartilage prior to development of frank histologic lesions and to examine the ankle joint for evidence of OA-like lesions.

Methods - Male Dunkin-Hartley guinea pigs (Charles River, MA) were divided by age into three groups of 8-10 animals each, 4, 7 and 10 months old. Animals were cared for in accordance with the procedures using lab animals as approved by the GlaxoSmithKline IACUC. After sacrifice the knees and ankles were removed, fixed in 10% formalin intact, decalcified and processed for histological analysis using a previously published scoring system\textsuperscript{4}. Histologic sections of the knee and ankle joints were stained with Safranin-O to assess the changes of proteoglycan (PG) amount or with hematoxylin and eosin. Sections were viewed for scoring surface integrity, PG staining, cellular changes, synovial membrane thickness, osteophyte formation and the presence of intraosseous cysts. Other sections were stained with picrosirius red FB3 and then viewed with a polarization microscope to reveal the optical properties of the extracellular matrix [i.e the presence or absence of birefringence indicating orientation of the collagen fibers\textsuperscript{5}].

Results - Focal histologic changes consistent with earlier reports were seen in the knees of animals at 4 months. In some animals focal areas of matrix swelling which correlated with a loss of Safranin-O staining, and an intact articular surface was noted. Most striking were alterations in the orientation of the collagen meshwork as revealed by picrosirius staining of histologic samples (Fig. 1 and 2). In areas where the articular surface remained intact, alterations in the orientation of the collagen meshwork just deep to the surface were seen suggesting changes in collagen: proteoglycan interactions not seen onroutine histologic preparations. These areas correlated with Safranin-O loss. A normal composite histology score is $6.0 \pm 0.5$. After 4 months, composite histology scores for the knees were $8.6 \pm 1.9$ and after 7 months were $11.3 \pm 2.6$. OA-like changes in the ankle were noted which included: disruptions in the articular surface, PG loss, alterations of the collagen meshwork, cyst formation, cell loss and areas of full thickness loss of cartilage (Figure 3). The presence of lesions among animals were more varied in the ankles. Composite histology scores at 4 months were $8.1 \pm 4.6$ and $9.2 \pm 4.6$.

Discussion – 1. Alterations in the collagen network are present in the early phases of the OA process and precede histologic changes in the articular surface. 2. OA-like changes in the ankle were noted. 3. Changes in the ankle were variable. 4. This is the first report of OA-like lesions occurring spontaneously in the ankle in the guinea pig.