Introduction

Osteoarthritis (OA) is prevalent in people and animals. As a result, this disease attracts considerable research attention. Many experimental models of osteoarthritis have been developed for research purposes using a number of different species. With each model, researchers strive to fulfill the goal of providing a clinically relevant and repeatable model of the disease.

The most frequently utilized experimental model for OA is the Pond-Nuki model of cranial cruciate ligament transection.[1,2] In this model, the cranial cruciate ligament of a dog is severed using a blind cut through a stab incision. This method produces moderate osteoarthritis in a species that is easily managed and develops osteoarthritis in a similar manner to that in human beings. The Pond-Nuki model has several limitations. The necessity of incising the joint capsule and allowing the severed ends of the cranial cruciate ligament to remain within the joint both contribute to the release of inflammatory mediators and the development of synovitis. The blind nature of the surgery can result in iatrogenic injury to the cartilage or menisci. Because of these factors, results of severity and progression of OA reported in the literature are variable.

In 1991, Inerot *et al* developed a model for arthritis in the canine hip joint by decreasing the amount of the femoral head covered by the acetabulum. They documented the development of OA using histologic and biochemical analysis. In this model, the joint is not opened, avoiding a disadvantage of the Pond-Nuki model. Evaluation of this model did not include force plate analysis, a research tool that has become important in objectively studying the response to treatment in OA research.

The purpose of this research effort was to further develop the model introduced by Inerot *et al* by standardizing the surgery, including more detailed radiographic evaluation, performing force plate analysis and subjective lameness evaluation, and verifying that radiographic and histologic evidence of osteoarthritic changes develop. The model was assessed for its suitability for use in evaluating efficacy of drug therapy for OA or other research applications investigating the pathophysiology of OA.

Literature Review

a. Pathophysiology of osteoarthritis

Osteoarthritis (OA) has been defined as "an inherently noninflammatory disorder of movable joints characterized by deterioration of articular cartilage and by the formation of new bone at the joint surfaces and margins".[3] This syndrome, because of similar clinical signs (pain, disability, swelling), must be differentiated from inflammatory arthritides. While OA does have an inflammatory component, it is not characterized by the influx of inflammatory cells seen in the other joint diseases. In human beings, OA has been estimated to affect 85% of the population between 70-79 years old.[4]

Since OA primarily affects the diarthrodial joints, a basic understanding of the anatomy and physiology of normal joint tissues is a prerequisite to further discussion. The typical diarthrodial joint is composed of two bones covered by articular cartilage and enclosed by a joint capsule containing synovial fluid.

Articular cartilage is the primary tissue involved in OA. The primary function of normal articular cartilage is to provide a smooth, durable, low-friction joint surface and to distribute load bearing from one bone to the other.[4-6] Cartilage is an aneural and avascular tissue composed of chondrocytes imbedded in an acellular matrix. The chondrocytes are not surrounded by lacunae but are in intimate contact with the surrounding matrix.[7]

Articular cartilage can be divided histologically into several zones, and the arrangement of chondrocytes gradually varies between these zones. The most superficial zone (farthest from the subchondral bone) is the tangential or gliding zone. In this layer the cells are flattened and elongated and are arranged parallel to the joint surface.[7,8] The transitional zone lies deep to the first and contains cells that are more rounded and arranged in a random manner.[7,8] This zone is the largest by volume.[9] Below the transitional zone is the radial zone where cells are arrayed in columns perpendicular to the tidemark, an irregular line at the junction of the noncalcified and the calcified regions of the cartilage that stains blue with hematoxylin and eosin.[7,8] The precise function of the tidemark is not understood. Beneath the tidemark is the calcified zone where the cells are arranged in columns in a calcified matrix. The calcified zone is supported by the subchondral bone plate. The calcified cartilage joins the subchondral bone at the osteochondral junction. The undulating nature of the osteochondral junction is important for transmission of force from articular cartilage to bone.

Hyaline articular cartilage is approximately 70-80% water by weight.[7] This water is dispersed throughout the matrix, and its presence depends upon the collagen and proteoglycan components of the matrix. The proteoglycan (PG) comprises approximately 35% of the matrix on a dry weight basis, and associated glycoproteins comprise an additional 10%.[8] The PG component of articular cartilage is found primarily in the transitional and radial zones. Proteoglycan is produced in the golgi apparatus of chondrocytes and is composed of a core protein to which sidechains of glycosaminoglycan (GAG) molecules are covalently attached .[2,10] The classic description is that the PG core and its associated GAGs resemble a test tube brush. The GAGs have a distinct negative charge associated with sulfate groups at their free end which results in the molecule being strongly hydrophilic.[7,8] Its negative charge also helps maintain the spatial structure of the cartilage under compressive loading. As a compressive load is applied to the articular cartilage the noncompressible water resists the force. If the force is maintained, the water is gradually expelled from the matrix resulting in a pattern of visco-elastic deformation.[6,10]

The majority of proteoglycan subunits in normal articular cartilage are bound by a link protein to hyaluronan.[7] Hyaluronan is a glycosaminoglycan that forms the backbone of a large (60-150 million daltons) molecule known as aggrecan.[7] There are four primary GAGs: chondroitin-4-sulfate, chondroitin-6-sulfate, keratan sulfate, and dermatan sulfate.[7] The two forms of chondroitin sulfate are longer than the other two GAGs.[7] The GAG types are not arranged randomly on the protein core but are consistently found in particular domains at certain distances from the link protein. Alterations to this arrangement form the basis of identifying the changes that occur to PG in articular cartilage in osteoarthritic joints, namely, that the amount of the chondroitin sulfate increases relative to keratan sulfate.[2] In normal cartilage, it is possible to extract only a small amount of PG with various solvents, indicating that the PG is firmly attached to the collagen network.[2] This contrasts with the situation in diseased joints suggesting that the PG is being disrupted and is less tightly aggregated.

Another major component of the articular cartilage matrix is collagen. Collagen molecules are designed in triple helices which form fibrils and fibers, serving to impart the majority of the tensile strength to the cartilage.[4,6] Type II collagen comprises as much as 90% of the total collagen in normal articular cartilage, but types I, III, V, VI, IX, X, and XI may also be present.[7-9] The collagen fibers are oriented uniquely in each zone of articular cartilage, and the orientation corresponds to the orientation of chondrocytes in that zone; for example, in the tangential zone collagen fibrils are parallel to the joint surface, in the transitional zone they are obliquely arranged, and the fibrils are perpendicular to the surface and the tidemark in the radial zone.[7,9]

Heterogeneity of the matrix is observed on the ultrastructural level with electron microscopy. The area immediately surrounding the chondrocytes, the pericellular matrix, contains a different glycosaminoglycan distribution than the matrix further from the chondrocyte. The pericellular matrix contains a higher percentage of chondroitin sulfate, whereas the interterritorial matrix, which is slightly further away, contains more keratan sulfate.[11] Additionally, the distribution of collagen types is location dependent. Type VI collagen is found in the pericellular region and may serve to link the cells to larger collagen fibers.[12]

Interactions between the various components of articular cartilage are complex and incompletely understood. The negative charge associated with the GAGs serves to maintain their spatial separation and contributes to the osmotic gradient.[8] The osmotic pull attracts water into the matrix from the synovial fluid.[8,9] The amount of water imbibed is limited in part by the elastic limits imposed by the collagen fibers.[9,10] The water, and the negative charge density, gives cartilage its ability to counter compression from load bearing by increasing turgor and evenly distributing the load.[8] The load bearing ability of cartilage is optimized by the damping effect of visco-elastic creep whereby during prolonged load bearing the water is slowly exuded from the cartilage.[8] The water forced from the cartilage also contributes to joint lubrication.[7] When the load is released, water slowly returns to the cartilage. This aids in the diffusion of nutrients and the elimination of cellular waste products. The role of this pumping mechanism in delivering nutrients to articular cartilage has been questioned.[13]

In addition to articular cartilage, a diarthrodial joint is composed of joint capsule, synovial fluid, and subchondral bone. The joint capsule is composed of several layers. Its outer, thick, fibrous portion, and surrounding connective tissue primarily fulfill a support role. The synovium, which is the inner layer, contains blood vessels and nerves and is important in maintaining the volume of synovial fluid. It is involved in various disease processes that affect joints.[8] The synovium has no basement membrane and may only be a

few cells thick in the normal patient. Synoviocytes are classified as either type A, which are mainly phagocytic, or type B, which are mainly secretory.[8] The synovial fluid itself is often called an ultrafiltrate of plasma because it is similar to plasma but does not contain many of the large molecules found in plasma.[8] In addition to maintaining joint homeostasis, synovial fluid also provides lubrication. The water that is forced out of the cartilage with compressive loads separates the opposing surfaces and provides a lubricating function. This is termed weeping lubrication. When no compressive loads are being applied, the synovial fluid itself provides a lubricating role through the actions of substances such as hyaluronic acid and lubricin.[8] This is termed boundary lubrication. It has been shown recently that the actual lubricant may be a surface-active phospholipid, while lubricin acts as a carrier molecule.[14]

The subchondral bone of the epiphysis is arranged in a lattice work configuration that allows for the transmission of forces of weight bearing from the articular cartilage cap to the cortex of the adjoining bone.[15] The cartilage is not connected structurally to the bone but interdigitates with subchondral bone at the osteochondral junction to provide a stable attachment.[10] This interdigitation allows shear forces to be converted to less destructive compressive forces. Subchondral bone is more pliable than cortical bone and therefore can more readily distribute the forces it absorbs. In diseased joints, the subchondral bone may become thickened or sclerotic, and this decreases its compliance thereby forcing the cartilage to absorb more forces of weight bearing.

The pathophysiology of OA has been studied extensively but is still incompletely understood. The disease process itself involves several events that interact to form a self-perpetuating and progressively more severe cycle. In many cases, an inciting event is difficult to identify. In animals, unlike in humans, OA without evidence of underlying causes is rare. Normal joints do not undergo deterioration with normal forces, however subjecting a normal joint to abnormal forces or the presence of normal forces acting on an abnormal joint may initiate OA.[8,16] In many researchers opinion, the primary pathophysiologic event in the progression of OA is PG loss, but this is not the inciting change.[10] Most commonly, OA begins with a disruption of the surface layer of the articular cartilage, and this physical damage initiates biochemical alterations that result in degradation of joint tissues.[10,17] Some researchers feel that the initial damage is not at the surface but rather involves loosening of the collagen bonds.[6,18] Mechanical conditions that result in uneven load bearings, such as gross incongruity of the joint, will result in concentration of loading to a particular part of the joint leading to abnormal wear.[10]

Disruption of the surface cartilage can occur for a variety of reasons. Regardless of the inciting event, this disruption initiates several changes. Surface disruption, which is termed fibrillation, resembles “flaking” on histologic evaluation because collagen fibers in this zone are arranged parallel to the joint surface.[19] Fibrillation initially causes disruption parallel to the collagen fibers, but with disease progression disruption becomes perpendicular to them. When integrity of the cartilage is damaged, its ability to transmit and resist loads is diminished. Initially the mechanical functions of cartilage are decreased due to increased water content secondary to loss of the restraining properties of collagen fibrils, and later becauase of general loss of matrix and the resulting cartilage thinning. This results in the initial fibrillation becoming fissures in the deeper layers of the cartilage. These physical disruptions may cause the collagen cross-linkages to break, which may in turn allow initial losses of PG.[18] Fibrillation also frees small fragments of cartilage matrix in the synovial fluid where they are phagocitized by the synovium. This causes an inflammatory synovitis.[20,21] Some experimental work has suggested that PG fragments may be the component responsible for the inflammatory synovitis.[22]

As fibrillation continues, chondrocyte damage occurs, and more proteoglycan is lost. Additionally, as the mechanical damage further degrades the weight distributing function of the cartilage, the subchondral bone is subjected to higher loads and responds by becoming more rigid and sclerotic and is less able to absorb and transfer forces from the cartilage to bone.[18,23] Without the protective mechanisms provided by a normal matrix, articular cartilage becomes more susceptible to further damage during normal weight-bearing and a vicious cycle of disease progression is set in motion.

Gross changes of an osteoarthritic joint depend on the severity of the disease, and, to some extent, the underlying cause. Initially, the joint capsule is thickened by fibrin and inflammatory edema secondary to the synovitis, and synovial villous hypertrophy may also be present.[7,24,25] Effusion is often present and is likely the result of increased vascular permeability secondary to inflammation, increased proximity of synovial capillaries to the joint space secondary to capsule stretching, or increased osmotic gradient associated with the increased cellular and protein content of the synovial fluid.[8] The cartilage surface often displays a dull appearance and may be pebbled and rough.[7] As degenerative changes progress, fissures may be evident, and ultimately, areas of cartilage erosion develop. The exposed underlying bone often takes on a polished appearance known as eburnation. Severe changes are first seen in areas of the joint most subject to the stresses of load-bearing; for example, the cranio-dorsal region in the canine hip.[7,26]

Osteoarthritic bony changes also occur both in the trabecular portion of the medullary canal and in the region of joint capsule attachment.[27] When an affected bone is sectioned longitudinally, it is noted that the trabeculae are dense and irregular, the cortex may be thickened, and the subchondral bone plate may be sclerotic.[7] At the point of joint capsule attachment and along the articular margin, bony proliferations known as enthesophytes and osteophytes, respectively, may develop. These proliferations become radiographically evident as they enlarge and ossify. The cause of this bony proliferation is not completely understood, but may represent an inflammatory response of the synovium and perichondrium, perhaps in response to stretching, or an effect of vascular ingrowth into the cartilage in the area.[8,28]

Histologic changes associated with OA are predictable based on the preceding discussion. Early changes include evidence of fibrillation of the cartilage and a decreased ability of the cartilage to take up metachromatic stains with a cationic charge.[2,8] This loss of metachromasia is indicative of loss of PG along with its characteristic anionic charge.[2,7] As fibrillation becomes more severe, vertical fissures develop. Chondrocytes exhibit cloning, an essentially pathognomonic finding in OA.[7] As the disease progresses, osteophytes become evident at the periphery of the joint. Changes in the joint capsule are variable. The subsynovium and synovium may be thickened or may be of normal cellularity. Both layers may show a marked inflammatory cell infiltrate.[7] Blood vessels may penetrate the tidemark, and in the more severe stages the cartilage may be completely absent in areas of high load-bearing.[8] The trabecular portion of underlying bone may show evidence of new bone formation, and the subchondral region is often thickened and sclerotic.[7,27,29]

Chondrocyte damage is significant in a number of ways. Despite the chondrocytes' ability to respond to and repair minor injury by increased anabolism, a point is reached where they can no longer compensate.[30] As their ability to maintain homeostasis is compromised, they begin to produce abnormal varieties of collagen and PG. Type I collagen, which is less biomechanically effective than type II collagen in weight distribution, may be produced. Some evidence suggests that crosslinking provided by type IX collagen may also be broken down.[8] The total water content of osteoarthritic cartilage increases due to loss of restraining tensile strength of the collagen fibers. This reduces the ability of the tissue to maintain its biomechanical properties.[6,8]

The PG produced in the osteoarthritic joint is less aggregated with shorter GAG sidechains. Despite increased synthesis of PG, there is a net decrease due to continuing loss.[22] PG loss results from the direct effects of physical damage to cartilage and from the actions of various degradative enzymes released by diseased chondrocytes.[10] Additionally, increased water content results in increased diffusion of large molecules such as PG, thereby contributing to their loss.[8] The actions of protease enzymes on PG include cleavage of the core protein and disruption of links to hyaluronic acid molecules.[30] This results in shorter PG molecules.

The synovial cells in an osteoarthitic joint also play a role in disease progression.[31] That synovitis observed in arthritic joints can either precede or follow cartilage change and implies several pathophysiologic mechanisms for degenerative joint disease.[32] This synovitis is likely secondary to exposure of neoantigens on the fragments or to other proinflammatory sequences on the cartilage.[25,33] Synovitis caused by phagocytosis of cartilage fragments prompts release of various biochemical mediators.[4,22] These mediators, or cytokines, stimulate the production of proteases by chondrocytes.[33] Synovitis is seen as early as one to eight weeks after injury in experimental models but is to less pronounced by 13 weeks.[20,31,32] Histologic changes observed in the synovium include a mononuclear cell infiltrate within one week, synovial cell pleomorphism by two weeks, and synovial cell foamy cytoplasm and vacuolation. These changes are most prominent at eight to 12 weeks in experimental OA.[20,34] Synovitis produced by arthrotomy can result in mild cartilage lesions consistent with early OA.[18,35,36] In general, however, the progressive lesions typical of natural and experimental arthritis appear to require some additional insult such as joint instability.[18,32,37]

As research on the pathophysiology of OA progresses, the importance of biochemical mediators and degradative enzymes has been established. There are a large number of enzymes that likely play a role in the disease. The primary ones belong to three families: serine, cysteine and metalloproteases. The metalloproteases may be the most important, especially those specific enzymes known as collagenase and stromelysin. Collagenase promotes the breakdown of collagen in the cartilage matrix, while stromelysen, along with acid proteases, primarily affects the PG.[38] In contrast to rheumatoid arthritis, where the enzymes seem to arise primarily from the synoviocytes, with OA the chondrocytes produce the majority of these enzymes.[30,38] Protease production by chondrocytes is supported by the fact that collagen destruction is initially pericellular. Chondrocytes that produce proteases seem to be located more densely in outer layers of articular cartilage.[33] The amount of collagenase recovered from cartilage is proportional to severity of lesions.[33] That the enzymes are produced by the chondrocytes themselves, and do not simply diffuse from synovial cells or other sources, was supported by further studies by Pelletier in which levels of the enzymes in the synovial membrane and in the cartilage did not correlate with each other.[31]

Degradative enzymes are initially produced in an inactive form and must be activated. Plasmin plays a vital role in activation.[33] Plasmin is formed in the inactive form plasminogen and must be transformed by plasminogen activator. Stomelysin likely plays a role in activating procollagenase to collagenase.[30]

Although the control of protease production is very complex and is incompletely understood, part of its regulation seems to be via inhibitor substances. Tissue inhibitors of metalloproteases are the best known and exist in at least two forms (TIMP-1 and TIMP-2).[30,38] Inhibitor substances interact with specific receptors which are currently being identified and characterized. In OA, the relative amount of TIMP is decreased, and therefore the enzymatic degradation of cartilage is allowed to progress. Plasminogen

activator (PA) also has an inhibitor (PAI), which ultimately serves to decrease the amount of plasmin and likely modulates the production of various cytokines and enzymes.[38] PA may itself have a direct degradative effect.[39]

Biochemical mediators, called cytokines, are vital at the most basic level of the disease process. In the normal joint, cytokines are integral in maintaining normal cartilage homeostasis.[30] Among the cytokines, interleukin-1 (Il-1), interleukin-6 (Il-6) and tumor necrosis factor alpha (TNF-α) have been most extensively studied. In the diseased joint, these mediators are believed to be released primarily by inflamed synoviocytes, chondrocytes and monocytes.[22,30,38] Interleukin-1 specifically has an inhibitory effect on TIMP and therefore indirectly promotes the degradative role of the metalloproteases.[4] Interleukin-1 likely also decreases the chondrocytes' synthesis of both collagen and PG while increasing the production of PGE_2.[30,38] Additionally, Il-1 activates macrophages and serves to stimulate the production of other inflammatory mediators and degradative enzymes by chondrocytes and synovial cells.[8] These individual actions of Il-1 may occur by completely different pathways, which complicates approaches to therapy.

TNF-α produces a variety of effects, many of which are similar to Il-1. It has direct and indirect catabolic effects on cartilage and may serve to activate Il-6.[30] Il-6, in turn, is less well understood. Although it seems to decrease cartilage matrix synthesis, particularly PG, it also may stimulate TIMP. Additionally, Il-6 may promote the formation of chondrocyte clones.[30] At present, control and regulation of cytokine production are only poorly understood.

Other mediators of inflammation that are of varying degrees of importance in the pathophysiology of arthritis exist. For example, the coagulation, kinin, and complement systems all have roles in the disease.[4] Activation of the coagulation cascade leads to the deposition of fibrin. Fibrin may also be produced in response to Il-1 and seems to be chemotactic for neutrophils. Neutrophils in turn, release elastase and cathepsin-G which degrade cartilage.[4] Activation of the kinin system may also occur with activation of the coagulation cascade; bradykinin is a mediator of pain and may cause bone erosion.[4]

In addition to these plasma derived systems, inflammatory mediators also arise from cell membrane-associated systems. Phospholipases can act on the cell membrane to cause activation of the cyclooxygenase and lipoxygenase cascades. The resulting prostaglandins and leukotrienes serve chemotactic and vasoactive roles as well as being involved as mediators of pain. Prostaglandins such as PGE_2 are found in increased concentrations in affected joints.[4]

The overall result of the combined effects of PG loss, chondrocyte damage, collagen changes, and activity of biochemical mediators is that the cartilage is weaker and therefore less able to function normally. This results in further physical damage to the cartilage and initiates a vicious cycle of painful arthritic disease.

b. Canine Hip Dysplasia

Canine hip dysplasia (CHD) is a disease, or disease syndrome, commonly affecting large breed dogs such as the Saint Bernard, Labrador Retriever, German Shepherd Dog, Old English Sheepdog, and Golden retriever. It is also noted occasionally in smaller breed dogs as well as in other species and human beings.[40,41] In people, a similar syndrome has been called congenital preluxation, congenital subluxation, congenital luxation, congenital dislocation, congenital displacement of the hip joint, congenital dysplasia of the hip, congenital hip dysplasia, and congenital acetabular dysplasia.[42] Unlike the disease in people, dogs with CHD have normal hips at birth.[26,43] Morphologic changes and clinical signs associated with CHD can begin as early as the first months of life and continue to progress. Although the underlying disease mechanism is widely believed to be physical, the pathophysiology of CHD quickly becomes that of osteoarthritis.

The clinical signs and the pathologic and radiographic changes associated with CHD were first described in the United States in 1935 which coincided with a dramatic increase in the popularity of German Shepherd dogs.[44-48] Similar clinical signs in man were reported by Hippocrates centuries ago.[49]

Canine hip dysplasia is prevalent in the at-risk population and presents a frustrating clinical problem for the veterinarian and owner. The clinical presentation is often biphasic, with young dogs presenting prior to one year of age due to pain caused by joint laxity, and older dogs presenting due to pain secondary to degenerative joint disease (DJD).[50] Clinical signs observed with CHD include exercise intolerance, reluctance to play or jump, pain upon manipulation of the hip, atrophy of pelvic and hind-limb musculature, and a variety of gait abnormalities. Diagnosis of CHD is often easily made from the signalment, presentation, and physical examination of the patient. Radiographic or post-mortem examination is necessary to confirm the diagnosis.[40]

Classically, a radiographic diagnosis has been made based on a ventrodorsal view of the pelvis obtained from the supine patient with the hind limbs fully extended.[40] This view is still the most widely recognized and most commonly performed, although severe degenerative changes can be noted on a variety of views. The Norberg angle is a measure of subluxation of the hip joint. The angle is defined by a line connecting the center point of both femoral heads on an extended-hip ventrodorsal radiograph and a line drawn from the center of the femoral head on the side in question to the cranial acetabular edge. In general, a larger angle suggests a deeper acetabulum and well seated femoral head. An angle of >105 degrees is frequently used to indicate normalcy. Conversely, an angle less than 90 degrees has been associated with poor hip conformation.[51] An alternate method of evaluating dogs for HD has been developed involving a stress-radiographic method.[52] This newer method has shown significant potential, and is especially important in the evaluation of young dogs.[52-55] From this work, the reliability of both the standard ventrodorsal view and the Norberg angle in predicting the development of degenerative joint disease has been questioned.[53] Regardless of the radiographic view, a diagnosis of HD is made based on the presence of subluxation, poor conformity between the joint surfaces, irregular shape, or presence of degenerative changes in the hip joint.

These degenerative changes may include changes to both the acetabulum and the femoral head and neck. Researchers do not whether the earliest degenerative changes arise from the cartilage, the subchondral bone, or the supporting soft tissue.[25] Subluxation is the first abnormality noted radiographically.[42,56,57] This can be observed as early as four weeks of age, or may not be demonstrable until the dog is considerably older.[40,48,58,59] As the disease progresses, bony changes become evident. These changes include thickening of

the femoral neck, flattening of the femoral head, a wider and shallower acetabulum, remodeling of the acetabular rim, and osteophyte production.[58,60]

Because of the subjective nature of evaluating radiographs for evidence of CHD, various investigators have devised objective systems of interpretation. The early system developed by Norberg to measure subluxation does correlate with joint laxity, but has been shown to be a poor predictor of future degenerative changes.[53] Because of this, an alternative protocol proposed by Smith has received a great deal of attention and may be the best method of evaluation.[52-55]

It is thought that the disease has three etiologic components: genetic, nutritional, and environmental. Although it has been proposed that environmental factors may play a dominant role in the clinical expression of the disease, dogs that are not genetically at risk are unlikely to develop primary lesions associated with HD.[61] Additionally, the heritability is not governed by simple Mendelian genetics, but is probably a complex multiple allele characteristic[48,50,62]. This complex genetic association is partially supported by, and partially explains, the lack of success in eliminating CHD by selective breeding, although numerous other factors also contribute to this lack of success.[41,61,63] Various studies have suggested an heritability of between 0.2 and 0.5.[50,61,63,64]

The role of pelvic muscle mass has received much attention, but remains unresolved. Riser and Shirer documented a correlation between pelvic muscle mass and occurrence of CHD.[65] They developed a pelvic muscle mass index scale to aid in identifying dogs likely to develop the disease. In an earlier study, Riser et al pointed out that within litters and sexes, dogs with higher early weight gain were more likely to develop CHD.[66] Based on these and other observations, some have concluded that CHD may be primarily the result of an imbalance in the rate of maturity of the skeletal and muscular components of the hip mechanism.[67] Other research has shown that histologic abnormalities are present in the pectineal muscle of dysplastic dogs, but myotomy of that muscle alone is not a preventative treatment.[68,69] The changes found in the muscle tissue are not predictive of CHD, and may even be secondary to the disease.[69,70]

Another possible contribution to the dysplastic condition is the nutritional influence. As has previously been noted, some correlation can be found when the rates of growth of dysplastic and nondysplastic dogs are compared.[66] There is also evidence that nutrition levels can be correlated to the development of other orthopedic diseases such as osteochondritis dissecans.[71] Various aspects of nutrition have been evaluated in relation to their role in the development of CHD, including total intake and electrolyte balance.[72-75] None of this work has shown nutrition to have more than a contributory role in the pathogenesis of CHD.

Environmental factors also influence the development of CHD. In man, it is known that positioning a child with the legs extended and abducted, as was done in cradleboards of certain American Indian tribes, will predispose the infants to dysplasia.[42] Also, in pups that were reared in strict confinement such that they were forced to adopt a seated posture that promoted coxofemoral reduction, the incidence of CHD was dramatically reduced.[44] Unfortunately, these dogs were socially unsuitable to become satisfactory pets. Some researchers have postulated that environmental factors are a more important contributor to the development of HD than genetics.[61]

Regardless of the importance attributed to the various etiologies, all these factors lead to the changes that are clinically recognized as CHD. The exact pathogenesis involved is not known. It is generally accepted that joint laxity is the initiating abnormality.[26,42,65] This has been supported by a demonstration that dogs with experimentally produced laxity

will develop HD.[76] The cause of laxity in the naturally occurring disease is not completely clear. Some researchers have noted the relation between hip laxity and an increased volume of synovial fluid.[25,57] It is unclear whether this volume increase is an inciting cause or a secondary change. It was shown, however, that withdrawal or addition of fluid to the joint would change the perceived laxity.[57] This finding was further developed with the discovery of a hydrostatic mechanism influencing hip laxity in which the closed system of joint capsule and synovial fluid prevent excessive displacement via the development of negative pressure when destractive forces are applied.[52]

Other possible causes of joint laxity include the discrepancy in muscle and skeletal developmental rates, or a myopathy of the pelvic musculature. Appropriate muscular development is particularly important since the hip is dependent on muscle support for stability.[23,42] It has also been noted that the triradiate bones of the acetabulum may fuse earlier than usual in dysplastic dogs, although whether this causes laxity or is caused by laxity remains open to speculation.[40,62,77] It is unlikely that any of these mechanisms is solely responsible for the hip joint laxity noted in CHD.

Joint laxity contributes to the progression of osteoarthritis in two ways. First, the unstable femoral head applies abnormal forces to the acetabulum during weight bearing since articular surfaces are no longer congruent.[78,79] Secondly, because joint congruity is necessary for normal joint development, the shape of the femoral head becomes abnormal.[10,40,42,62] During the first 60 days of life this deformation can be profound.[77] Femoral head malformation results in abnormal forces on the acetabular surfaces.[78,79] These mechanical stresses initiate the process of cartilage degradation described previously.

Changes that occur within the abnormal hip joint include thickening of the ligament of the femoral head, medial displacement of the greater trochanter of the femur and the development of a shallow acetabulum.[26] These changes result from abnormal forces occurring within a lax joint. The deformed femoral head applies pressure to the acetabular articular surfaces, and the subchondral bone in the area of increased load remodels and becomes sclerotic. With time, the pressure causes fibrillation of articular cartilage and subsequently fissures and microfractures. As the articular cartilage is damaged and worn away, the femoral head becomes eburnated, the shallow acetabulum covers less of the femoral head , the joint capsule thickens and osteophytes develop on both the femoral head and the acetabulum. Eventually, the ligament of the femoral head tears completely, is resorbed, and bone fills the acetabulum.

c. Experimental models of osteoarthritis

Because OA is a debilitating disease that affects the human population at large, research into its cause and treatment attracts considerable attention. Some biochemical studies are conducted on isolated tissue samples, but the majority are performed on live animal models in order to accurately evaluate the dynamic disease process. Whether in animals or in human beings, research using patients with naturally occurring disease (i.e. not created experimentally) has severe limitations.

Ethical considerations limit the assignment of patients into treatment and control groups. Clinical patients are understandably unwilling to allow significant tissue sampling. In most naturally occurring cases, the starting point of the disease is often unknown or the history is incomplete, and it is difficult to definitively place patients in experimental groups chronologically. Researchers, therefore, are often limited to studying cases of more chronic, naturally occurring, disease. The presence of confounding concomitant disease processes is always a complicating factor.

The above considerations lead to the desirability of using animal models in the study of OA. The use of animal models permits the investigator to work from a known starting point and etiology in the development of a disease, study the early changes that occur in the course of the disease, study the progression of the disease, document progressive pathology, and minimize patient and disease variability.

The ideal experimental model for the study of OA has not yet been developed, but it would have several characteristics. It should closely mimic the naturally occurring disease, have a consistent expression, have obvious pathologic changes in the early stages of the disease, and be easily studied. The creation of the model should be relatively simple and ethically appropriate. The onset of disease should occur in a reasonably short period of time so that costs are minimized. Finally, the animal species used should be readily available and manageable.

Several animal species have been used for creating experimental models of OA. Mice are advantageous for several reasons. They breed readily, and are easy and inexpensive to house. Some strains of mice have a high incidence of naturally occurring primary osteoarthritis.[2] This congenital arthritis arises from genetic defects in the cartilage, and thus has a different etiology than the most common forms of the disease in man. Caution should be exercised in applying results using this model to other species. Their use, however, presents several problems. Only a very small amount of cartilage is available for the study from affected joints. Also, fundamental differences exist between OA in mice and human beings. Not only do mice differ from human beings in the osteochondral ossification process, but differences also exist in the composition and structure of proteoglycan.[2]

Guinea pigs provide a slightly larger research animal, and are still economical to feed and house but provide small sample volumes. Schwartz describes a guinea pig model in which an arthrotomy is performed and the cranial cruciate ligament and medial collateral ligament severed to produce instability.[80] Other arthritis models using guinea pigs were developed by resection of portions of the gluteal muscles or transection of the infrapatellar ligament.[81]

Rabbits have also been used extensively in OA research. Rabbits share many of the economic advantages of mice and guinea pigs, while allowing more adequate tissue sampling. The majority of experimental models using rabbits involve the creation of instability in the stifle joint. Instability alters the forces to which articular cartilage is

subjected and therefore creates physical damage. These models utilize varying degrees of surgical manipulation to create the instability, and therefore cause varying degrees of trauma to the joint and subsequent synovitis. This trauma may alter the catabolic environment within the joint influence the progression of the disease, and create differences from naturally occurring OA. This will be discussed more fully later.

An early model of OA using rabbits first reported by Hulth et al and by Telhag and Linberg, involved ligament transection.[82,83] These investigators transected the medial collateral ligament and both cruciate ligaments, and removed the medial meniscus. The changes that occur in this have been well described. The procedure results in a rapid, marked change from the normal joint, and therefore may not result in an accurate reproduction of the naturally occurring disease. A modification of this procedure has been described where the lateral collateral ligament, lateral meniscus, and sesamoidean ligaments were sectioned.[84]

The most recently developed rabbit model involves either partial or total meniscectomy. This procedure was used by Moskowitz who noted consistent onset of degenerative changes within twelve weeks.[85,86] Other investigators have studied this model and have produced a variety of modifications including the method and amount of tissue removal or damage.[86] In general, rabbit meniscectomy models produce a mild form of OA, but the disease severity and progression is highly dependent on the amount of trauma caused by the surgical procedure, particularly as it relates to the synovium.[2]

Joint immobilization has been used to create arthritic change in a variety of species, and has involved immobilization in flexion and extension, and with an external force applied across the joint.[86] The concept was first used in rat stifles, using an internal plexiglass splint passed under muscle and attached to the femur and tibia to immobilize the joint.[87,88] This model produced mild changes, but is still limited by the amount of tissue available for study. Immobilization of the stifle joint in rabbits produces predictable changes, although controversy exists as to the permanence of the degeneration.[86] The creation of disease in immobilized joints is likely dependent on the loss of nutrition to chondrocytes, and therefore has fundamental differences from naturally occurring OA. Instead of being activated early stage of OA, the chondrocytes in immobilized joints degenerate and die.[86] Other researchers have used repeated loading of rabbit stifles over time to produce OA.[17,89] These procedures result in OA, but are time consuming.

The dog is the most common species used in the study of OA. Dogs are generally easy to work with, readily obtainable, and of a size to provide appropriate sample volumes. OA models in the dog have been created by the intraarticular injection of noxious substances, by the creation of stifle instability following transection of the cranial cruciate ligament, and by surgically altering the shape of the pelvis to produce OA in the hip joint. It should be noted that models involving the injection of noxious substances into a joint produce a primary synovitis that results in secondary damage to the cartilage. This is not the same as OA in which the damage to the cartilage occurs first and the synovial inflammation is secondary. This difference is important in applying results from research studies to clinical cases of OA.

The most common canine model of OA is the Pond-Nuki model which creates stifle instability by transection of the cranial cruciate ligament.[1] Rupture of the cranial cruciate ligament occurs naturally in many species, including man and the dog. Adaptation of this injury was first used experimentally by Marshall in 1969. He performed an arthrotomy to sever the ligament, and then studied the onset of disease with a primary focus on the development of osteophytes.[28,90] This model was further refined by Pond and Nuki in 1973. These investigators advocated transection of the ligament using a blind stab incision

in order to simplify the procedure and limit synovial damage.[1] The experimental disease is believed to mimic the naturally occurring condition, and to result in lesions that are consistent to each other in location and rate of development.[2]

Factors that limit the Pond-Nuki model from completely fulfilling the criteria of the ideal OA model[24,91] include the fact that the joint capsule is penetrated surgically which creates a degree of synovial inflammation.[2,24,34] Since this synovitis is primary, and not secondary to cartilaginous change, it may not truly recreate the natural condition. In support of the Pond-Nuki model, the significant degree of inflammation found in the experimental joints is not always noted in knees undergoing only a stab incision with no instability created (a sham surgery).[31,36] If, at the time of necropsy, the inflammation was not consistently found in the sham-operated joints, one could assume that it disappeared early in the studies, and thus did not likely contribute to the disease pathophysiology during the entire study. One could still not speculate as to its contribution to the early stages of disease. Whether the synovitis in the arthritic joint is due to trauma secondary to instability or is an integral part of the natural disease, or both, is not entirely clear.[31,92,93] It is known that dogs with naturally occurring cranial cruciate ligament rupture, develop a thickened and hypervascularized joint capsule.[34,94] The relative roles and importance of mechanical versus inflammatory factors in the progression of OA has yet to be answered.[95] In regard to the degree to which the synovitis affects disease progression, it should be noted that in a long term study by Marshall and Olsson the joint capsule was noted to markedly thickened with fibrous tissue at six to eight months post-operatively. The same investigators did not remark on any inflammatory infiltrate at that point.[90] This may indicate that the changes in the capsule had stabilized and were no longer contributing to the joint disease, although the description was not detailed enough to rule out continuing inflammation. Again, this suggests that synovial inflammation accompanies arthrotomy and instability, but the duration remains unknown. There is synovitis associated with the Pond-Nuki model, and this may be significant in producing OA, but there currently is insufficient data to definitively remark on its significance in disease progression.[36]

Another source of inflammation is the presence of cruciate ligament remnants in the joint. Cutting the ligament using a stab incision results in bleeding from the small vessels on the ligament surface which contributes to the inflammation.[24] These ligament fragments, which cannot be removed through a stab incision, persist until degraded by inflammatory processes. This also occurs in the natural cruciate rupture in dogs, however in order to replicate spontaneous OA as it occurs in man, it would be desirable to avoid these confounding variables.

Although many researchers describe similar lesions using the Pond-Nuki model, others report a wide variation in time of onset and severity of pathologic changes with the Pond-Nuki model.[91,96-98] This is likely related to variables such as surgical technique, iatrogenic damage of other joint structures and variation in the experimental protocol. The amount of damage to joint structures other than the cranial cruciate ligament when a stab incision is used to transect the cranial cruciate ligament is variable and unknown. In one investigation, researchers used an arthroscopic technique to perform the ligament transection; the difference between this method and the standard stab incision was not assessed.[99] McDevitt reported in one study that occasional damage to the articular cartilage was caused by the stab incision.[34] Other factors that could influence the outcome include animal weight, age and breed, the time between surgery and evaluation, and the amount of exercise allowed.[91] Palmoski showed that immobilization dramatically affects the development of osteoarthritis in this model by eliminating some of the instability.[100]

The variability in time of onset and severity of lesions noted in different studies likely relates to the aforementioned technical variations. Investigators from one institution

have achieved consistent results.[34,96,97,101,102] McDevitt's work in 1977 is typical. The investigators noted that gross and histologic changes were present as early as one to two weeks after surgery, and included thickening and softening of the cartilage as well as roughening of its surface.[34] They observed complete focal cartilage disruptions by four weeks, and histologic evidence of erosions at 16 weeks. They also noted a thickened synovium by three weeks, and osteophyte production by two weeks. In contrast, in another study in which the ligament was cut via arthrotomy, osteophyte production was first documented 26 days post operatively.[28] That study documented moderate cartilage thickening by 4 weeks, and erosions at 6 weeks post-operatively. Still other investigators have reported less severe changes as late as 27 weeks or even eight months post-operatively using the same model.[91,98] Marshall and Olsson reported mild cartilage changes at six to eight months and with no erosions of articular cartilage.[90] One study noted that the cartilage was thickened and consistent with reversible change three years after surgery.[103] The changes in the stifles may cease to progress as would occur in the natural disease.[104] This has prompted some investigators to consider the Pond-Nuki model one of reversible injury and subsequent repair than of OA.

In contrast, in the study with the longest follow up to date, Brandt *et al* showed that after a period of 54 months post-surgery, the changes following cruciate ligament transection were progressive and included full thickness erosions.[105] These researchers also noted mononuclear cell infiltrate in some regions of the synovium, suggesting chronic inflammation. Similar findings were noted after a shorter study in which investigators observed inflammatory cell infiltration of the synovial membrane to be present at eight and sixteen weeks following severance of the ligament.[20] Even mild synovitis can affect joint function and will decrease the accuracy with which a model reproduces clinical OA.[106] Synovial inflammation is not necessary for the development of OA, as shown in models that involve increased repetitive loading of a joint.[107]

The degree to which operative synovial damage alters the pathophysiology of degenerative joint disease has been studied, but no firm conclusions have been drawn. There is no question that following surgical invasion of a joint, even one as mild as that used in the Pond-Nuki model, inflammation results. This inflammation has been shown to affect both the synovium and the cartilage. It is widely accepted that, by itself, this inflammation will not result is serious joint disease, since sham surgeries in dogs do not cause OA.[34] Conversely, Lukoschek *et al* found that cartilaginous changes did occur in the knees of rabbits undergoing arthrotomy without destabilization, and these changes were progressive.[35] These researchers found mild changes including effusion, synovial histologic changes (synovial cell hypertrophy and inflammatory cell infiltrate), and mild progressive degeneration of the cartilage. Cartilage lesions were noted within one week of arthrotomy.[35] Frost and Ghosh showed that microinjury caused by the intraarticular injection of saline resulted in cartilage damage.[108] In attempting to study the role of synovial factors on the development of OA, Pelletier et al found that synovial inflammation correlated with the collagenolytic activity of cartilage, suggesting that the synovium can have a significant effect on the development of OA.[31] In other work, it has been shown that although synovial changes occur subsequent to arthrotomy, these changes are mild and appear to resolve before they result in OA.[20]

Following transection of the cranial cruciate ligament, dogs may develop tears of their medial meniscus which can compromise the Pond-Nuki model. This may occur at various times post-operatively, provides an additional cause of lameness and inflammation,[109] and interferes with interdog comparisons. Tears in the medial meniscus occurred in all dogs in one study by eight months post surgery, but the times when the tears occurred post-operatively were not determined.[90]

Inerot *et al* attempted to create OA in the hip joint of the dog by altering the amount of acetabular coverage of the femoral head. Estrogen given in high doses to young dogs creates laxity and the subsequent development of degenerative change.[110,111] Additionally, Riser created a condition similar to naturally occurring canine hip dysplasia by severing the external rotator muscles of the hip.[26] This investigation was compromised by only five dogs being evaluated, all young German Shepherds and control hips developed evidence of dysplasia also.

In the model developed by Inerot *et al*, the orientation of the acetabulum was altered to change the biomechanics of the hip joint to mimic hip dysplasia.[112] The acetabulum was mobilized with three osteotomies, and screws used to stabilize the bones a position that resulted in less coverage of the femoral head. This procedure is the reverse of the triple pelvic osteotomy surgery used in human beings and dogs to treat hip dysplasia. One of the advantages of this model is that the joint is not opened, and therefore no direct iatrogenic cartilage damage or synovitis is caused. The procedure was performed on thirteen dogs which were killed at varying intervals to evaluate histologic and biochemical change. Histologically, changes typical of OA were noted which appeared to worsen with increasing time post-operatively. Decreased amounts of GAGs were noted in the cartilage, and the PGs were smaller and less able to aggregate. Deficiencies in the study including a lack of complete descriptions of the radiographic changes, the number of animals, and management influences has limited widespread application of the results and the technique. Because of these shortcomings, the model requires additional testing as a repeatable standardized OA model in order to validate it as a useful vehicle to study OA in a research setting.

d. Force plate evaluation

Evaluation of kinetic data obtained from force plate analysis plays an important part in veterinary orthopedic research.[113-125] Researchers have used force plate analysis to investigate gait, development of lameness, response to therapy, and drug efficacy, among other topics. The chief advantage of force plate analysis is that the results are objective instead of relying on an observers skill and bias in assigning a subjective lameness score.

A force plate is a measuring device that records and displays the force exerted by a subject during ambulation. These "ground reaction forces" exerted by a limb can be measured in three orthogonal axes: vertical, lateral (right or left), and craniocaudal (propulsion and braking). Braking represents the force necessary to decrease the momentum of the subject after the paw initially contacts the ground. Propulsion is the force necessary to increase the momentum of the subject, or accelerate, as the gait cycle continues.[126] In order to collect this data, a handler leads the subject at a steady gait across the force plate platform. In veterinary medicine, the force plate itself is placed flush to the walking surface, and is not identified by any features that could distract the animal. As the subject is led across the plate, care is taken to ensure that a steady pace is maintained, and that the animal does not make any motions that might alter the forces applied by a particular limb. Passes across the plate (or trials) are recorded on video tape and reviewed prior to accepting the trials. Inappropriate foot placement or motions that alter the ground reaction forces are among the reasons a trial might be discarded. Different handlers can be used at different time periods for the same dog and not alter data.[127] After data are reviewed for obviously nonrepresentative limb strikes, the values can be evaluated.

A number of trials are obtained, and the combined data for a given time period are compared to other time periods or to other treatment (surgery, drug therapy, etc.) groups. The values commonly evaluated in veterinary medicine include the peak force (maximum value recorded during the stride) and impulse (the area under a curve charting force over time) in the vertical and craniocaudal directions. Both peak force and impulse values are generally reported as unitless numbers and are based on a percentage of body weight (peak force) or a percentage of body weight multiplied by the time (impulse). When subjects are lame, the values for these categories are decreased in comparison to previous time periods or to other treatment groups.

Experimental Design and Methodology

a. Dogs:

Twelve adult mixed breed dogs ranging in weight from 19.1kg to 31.8kg were used. All dogs were judged healthy based on physical examination and routine pre-surgical blood work (packed call volume, total solids, and blood urea nitrogen estimate[a]). Additionally, none of the dogs had evidence of pre-existing orthopedic disease as evaluated by physical examination and pelvic radiographs. All dogs were housed in 1.5 X 3 meter runs and exercised outside on a leash at a trot for 15 minutes six days each week except on days when force plate data was collected and for the two weeks following surgery. All procedures and evaluations were approved by the Animal Care and Use Committee of Virginia Tech.

b. Surgery (Figs. 1-8):

Dogs were randomly assigned to either a sham-operated group or an acetabular rotation group. Dogs were paired by body size to eliminate bias from body weight variations. The dogs were premedicated with acepromazine[b] (.02mg/kg IV) and butorphanol[c] (.1mg/kg IV) prior to anesthesia induction with thiopental[d] (15mg/kg IV to effect). Anesthesia was maintained with isoflourane[e] delivered via an endotracheal tube. An epidural injection of preservative-free morphine[f] (.15mg/kg) was administered aseptically to minimize required concentrations of inhalation anesthetics and provide postoperative analgesia . The left hindlimb and pelvis was prepared for aseptic surgery.

Dogs assigned to the acetabular rotation group underwent three pelvic osteotomies performed through separate incisions as described by Slocum.[128] A ventral approach was made to the pubis and a 1 cm segment of bone was removed. A caudal approach to the ischial plateau was performed and an osteotomy into the obturator foramen was performed using gigli wire. Finally, a lateral approach to the ilium was performed via a gluteal roll-up technique[129] including transection of the cranial gluteal artery, vein, and nerve, and a mid-body osteotomy of that bone was performed after a right 45° pelvic osteotomy plate[g] was contoured to fit the ilium. Following the ilial osteotomy the pelvic osteotomy plate was applied. These plates are designed to increase the amount of acetabular coverage of the femoral head when applied to treat hip dysplasia, and are specific for the left or right side of the pelvis. By applying a plate designed for the right side to the left ilium the opposite result was achieved, that is, decreased coverage of the femoral head. The primary investigator (WCR) was not present during application of the bone plate, and remained blinded to which treatment group a dog was assigned. ASIF recommendations for plate size were followed; five dogs received 3.5 mm bone plates, and one dog received a 2.7 mm bone plate. All incisions were closed routinely. The skin sutures were removed after 14 days.

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[a] Azostix®; Bayer Corp, Elkhart, IN
[b] Acepromazine® Fort Dodge lab Inc., Fort Dodge, IA
[c] Torbutrol® Fort Dodge lab Inc., Fort Dodge, IA
[d] Pentothal Abbot, N. Chicago, IL
[e] Isoflo Solvay, Mendota Heights, MN
[f] Duramorph®; Elkins-Sinn, Cherry Hill, NJ
[g] Triple Osteotomy Plate; 45°, Synthes (USA), Paoli, PA

Model Demonstrating Osteotomies and Plate Application

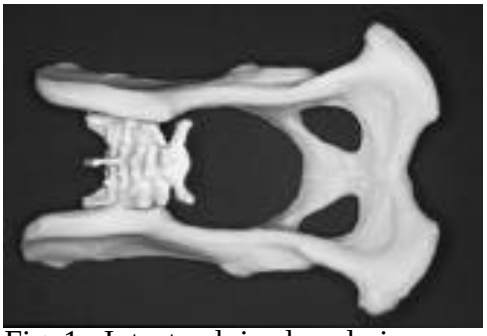
Fig. 1: Intact pelvis, dorsal view

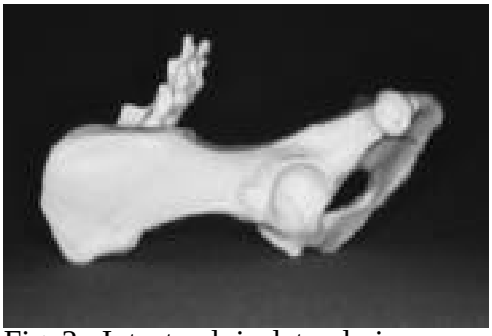
Fig. 2: Intact pelvis, lateral view

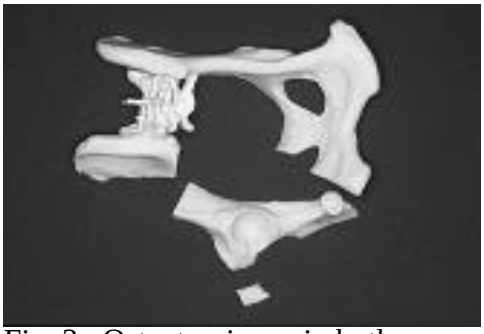
Fig. 3: Osteotomies as in both groups

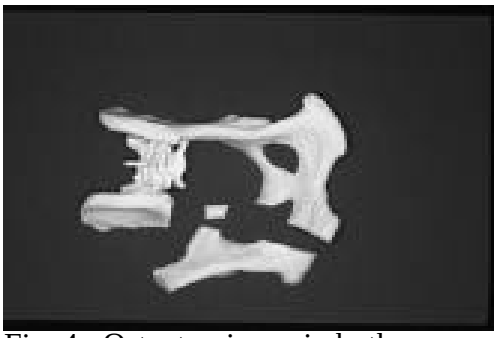
Fig. 4: Osteotomies as in both groups

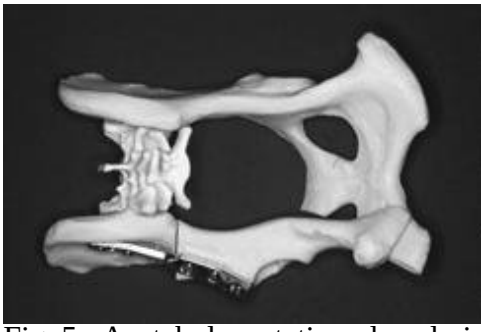
Fig. 5: Acetabular rotation, dorsal view

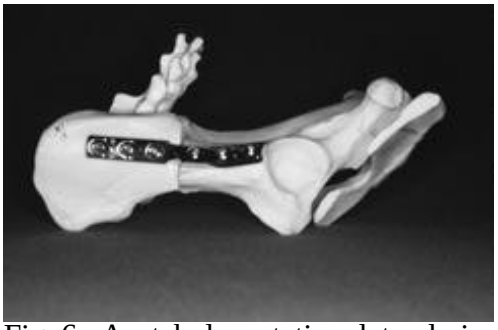
Fig. 6: Acetabular rotation, lateral view

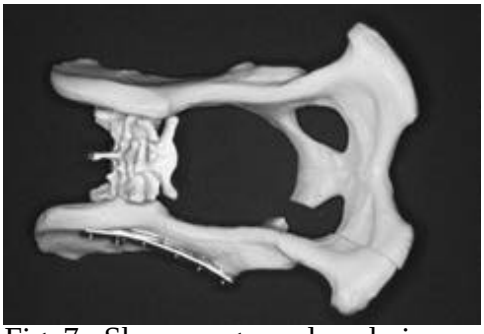
Fig. 7: Sham-surgery, dorsal view

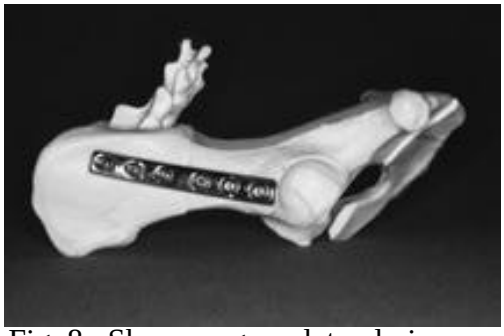
Fig. 8: Sham-surgery, lateral view

Dogs in the sham operated group underwent identical surgical procedures except that a six-hole dynamic compression plate[h] was used to maintain the ilial fragments in an anatomic relationship. ASIF recommendations for plate size were followed, resulting in an identical distribution of plate sizes compared to the first experimental groups. During the perioperative period, all animals were prophylactically treated with a first generation cephalosporin[i] (22mg/kg IV q2hr).

Following surgery, each animal was radiographed while anesthetized to evaluate surgical repair, monitored during recovery and returned to their runs when ambulatory. All dogs were monitored for evidence of discomfort and additional pain medication administered if needed. Each dog received acetominophen and codeine[j] (1mg/kg codeine PO TID) for three days post-operatively, and was not exercised for two weeks. The dogs were then returned to their regular exercise schedule.

c. Radiographic evaluation:

Each dog was evaluated radiographically and had no radiographic evidence of osteoarthritis or laxity in the coxofemoral joint pre-operatively. Radiographic assessment was performed at 4, 8, 12, 16, 20, and 24 weeks post-operatively. Each radiographic assessment was conducted with the dog heavily sedated with a combination of atropine[k] (.02mg/kg IM), xylazine[l] (.05mg/kg IV), and butorphanol[m] (.1mg/kg IV). Radiographs of the pelvis included left lateral view, ventro-dorsal view with hips extended, and ventrodorsal view with hips at 90 degrees and abducted ("frog legged"). In the hip-extended view, particular attention was given to assuring symmetrical, parallel positioning of the femurs to assure accurate and consistent placement. In the "frog-legged" view, emphasis was placed on alignment of the ilial wings in a symmetrical manner to assure that the pelvis was consistently radiographed in the same position. The radiographs were all evaluated for evidence of degenerative joint disease (presence of osteophytes, remodelling of the femoral head or neck, shallow acetabulla). The ventrodorsal views with hips extended were evaluated to determine the Norberg angle for each hip. The frog-legged views were evaluated using a computerized digital image analysis system[n] to determine the amount of acetabular coverage of the femoral head. This coverage was then compared to the pre-operative values based on the percentage change in the surface area.

d. Evaluation of lameness

Each dog was evaluated by assigning a subjective lameness score and by force plate analysis at 2, 4, 6, 8, 12, 16, 20, and 24 weeks post-operatively. The subjective lameness scoring method was modified from one used by Holtsinger[130] (Table 1). All lameness evaluations were performed by one individual who was blinded as to experimental groupings.

Force plate evaluation was performed on a 40-foot walkway with the force plate[o] mounted in the center of the walkway and flush with the surface . Three photoelectric timing devices and the force plate were connected to a dedicated computer and software

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[h] DCP® Dynamic Compression Plate; Synthes (USA), Paoli, PA

[i] Cefazolin Sodium; Marsam, Cherry Hill, NJ

[j] Acetaminophen 300mg with Codeine Phosphate 60mg

[k] Atropine Sulfate; Amvet Scientific Products, Yaphank, NY

[l] Rompun® Bayer, Turner, KS

[m] Torbutrol® Fort Dodge lab Inc., Fort Dodge, IA

[n] Cue-3® Olympus, Lake Success, NY

[o] AMTI OR6-6;

Table 1: Lameness score*

A. Lameness
1= stands and walks normally
2=stands normally, slight lameness at walk
3=stands normally, severe lameness at walk
4=abnormal posture when standing, severe lameness at walk
5=reluctant to rise and will not walk >5 strides

B. Weight-bearing
1 = normal weight-bearing on all limbs at rest and when walking
2 = normal weight-bearing at rest, favors affected limb when walking
3 = partial weight-bearing at rest and when walking
4 = partial weight-bearing at rest, non-weight-bearing when walking
5 = non-weight-bearing at rest and when walking

C. Joint mobility
1 = <15 degree limitation of hip extension
2 = 15-30 degree limitation of hip extension
3 = 30-45 degree limitation of hip extension
4 = 45-60 degree limitation of hip extension
5 = >60 degree limitation of hip extension

D. Willingness to hold up contralateral limb
1 = readily accepts contralateral limb elevation, bears full weight on affected limb >2 min.
2 = offers mild resistance to contralateral limb elevation, bears full weight on affected limb >1 min.
3 = offers moderate resistance to contralateral limb elevation and replaces it in 30 sec. or less
4 = offers strong resistance to elevation of contralateral limb and replaces it in 10 sec. or less
5 = refuses to raise contralateral limb at all

E. Pain
1 = no pain elicited on palpation of affected joint
2 = mild pain elicited, e.g. turns head in recognition
3 = moderate pain elicited, e.g. pulls limb away
4 = severe pain elicited, e.g. vocalizes or becomes aggressive
5 = will not allow examiner to palpate joint due to pain

* adapted from Holtsinger[130]

program[p]. A video camera was used to record all trials. All dogs were evaluated using a velocity range of 1.60 to 1.90 m/s and an acceleration range of +/- 0.5m/s/s. As the handler trotted each dog across the platform, an observer noted whether each trial was acceptable. Trials were later reviewed on videotape to confirm the observer's assessment. An acceptable trial consisted of a pass across the forceplate that included distinct foot strikes by the left or right forelimb and the ipsilateral hindlimb and was within control

[p] VBEL; Sharon software

values for velocity and acceleration. Trials were discarded for distracting head motions or irregularities in gait. Trials were collected until five acceptable trials were obtained for each side, and the mean of the five trials was calculated for statistical evaluation. Each dog was evaluated three times pre-operatively with no less than three days between evaluations, and data were averaged to obtain baseline values. Force plate data were analyzed with regard to difference from the preoperative value and the difference between surgery groups. Peak force (PF) and impulse (IF) were recorded in the vertical (PFz and Ifz) axis as well as propulsion (PFYb and IFYb) and braking (PFYa and IFYa) in the craniocaudal axis.

e. Necropsy

Each dog was humanely killed with an overdose of pentobarbital phenytoin[q] at the conclusion of the study. Muscles and implants were carefully removed from each pelvis, and the joints removed along the lines of the original osteotomies. Synovial fluid was carefully aspirated, and replaced with formaldehyde using a syringe and 22 gauge needle. The hip joints were submerged in formaldehyde at a volume to volume ratio of approximately 9 to 1. The formaldehyde in the joint was changed after approximately 10 days.

f. Histologic evaluation

The isolated hip joints were trimmed to include a coronal section of the hip joint at the level of the ligament of the femoral head, including the adjacent acetabulum. A piece of joint capsule was harvested at the same level. The bone sections were place in a decalcifying solution,[r] processed via an automated tissue processor,[s] and imbedded[t]. The samples were sectioned to a thickness of 5 μm, stained with alcian blue and with hematoxylin and eosin and then evaluated according to the Modified Mankin Score (Table 2). The joint capsule samples were stained with hematoxylin and eosin and evaluated (Table 3). The histologic evaluations were done by one pathologist who was blinded as to the treatment group and side of the animal from which the tissues originated.

[q] Beuthansia-D Special®; Sjering-Plough Animal Health corp., Kenilworth, NJ
[r] TBD2; Shandon-Lipshaw, Pittsburgh, PA
[s] Miles Scientific VPI Automated Tissue Processor; Sakura, Torrence, CA
[t] Surgipath EM 400 Imbedding Medium; Surgipath Medical Industries, Richmond, IL

Table 2: Modified Mankin Scale Used in Histologic Grading of Articular Cartilage[131]

Structure		
	Normal	0
	Irregular surface, including fissures into the radial layer	1
	Pannus	2
	Superficial cartilage layers ($\geq$6) absent	3
	Slight disorganization (cellular rows absent, some small superficial clusters)	4
	Fissures into calcified cartilage layer	5
	Disorganization (chaotic structure, clusters, osteoclast activity)	6
Cellular abnormalities		
	Normal	0
	Hypercellularity, including small superficial clusters	1
	Clusters	2
	Hypocellularity	3
Matrix staining		
	Normal/slight reduction	0
	Staining reduced in radial layer	1
	Reduced in interterritorial matrix	2
	Only present in pericellular matrix	3
	Absent	4

Table 3: Joint Capsule Evaluation

Histopathologic Score	Interpretation
0	normal, unremarkable
1	slight increase in synovial membrane cellularity or reactive villar hyperplasia, slight increase in vascularity, or inflammation
2	moderate changes to criteria above
3	severe changes to criteria above

g. Statistical analysis

Force plate data, Norberg angles, and femoral head coverage measurements were all compared between treatment groups at each time interval, including pre-operatively and between the left and right limbs at each time interval. Because the subjective lameness score did not evaluate each leg independently, this data was only compared between treatment groups, between each time period and the preoperative values. The histologic data was evaluated by comparing the treatment groups and by comparing the left hips to the right within each treatment group.

All data comparisons were performed using a repeated measures test with a level of significance of $p=0.05$.

Results

All dogs recovered from surgery uneventfully and were weight-bearing-lame during the course of normal activity for the duration of the study. All dogs were willing to exercise readily by the second week post-operatively, and no surgical complications associated with the experimental protocol were observed.

a. Radiographic evaluation:

Upon radiographic examination, no evidence of bone movement was noted during the healing process. The majority of dogs had bridging callous by 12 weeks post-operatively and lack of visible fracture line by 16 weeks post-operatively, although some healed without callus formation. Several dogs experienced screw loosening but no gross displacement of bone plates resulted. Screw loosening is a common finding following triple pelvic osteotomies in the clinical setting.[132,133] Evaluation of the ventro-dorsal radiographic projections did not reveal evidence of OA in the coxofemoral joint.

Evaluation of coverage of the femoral head by the acetabulum indicated statistically significant difference from the pre-surgical values at all time periods except at eight weeks for the left hip in the acetabular rotation dogs (Table 4, Fig. 9). A difference from the pre-surgical values was also noted at two time intervals in the sham-operated group and once in the nonoperated right hip of the acetabular rotation dogs. When the two surgery groups were compared, it was noted that a significant difference was present in the left hip at all time periods from four weeks post-operatively until the conclusion of the study. A statistically significant change existed between the right and left hips of the acetabular rotation group at all time periods, but not in the sham-operated group. Frequently, the placement of the bone plate (either treatment group) was found to impinge slightly on the radiographic projection of the acetabular margins. When this occurred, an effort was made to project where the margin would lie if it were not obscured.

Table 4: Percentage difference in coverage of the femoral head compared to pre-operatively

Time Period (weeks)	Rotation Group				Sham Group			
	Left leg		Right leg		Left leg		Right leg	
	mean	STD	mean	STD	mean	STD	mean	STD
Pre-operative	0	0	0	0	0	0	0	0
Post-operative	.28*$	.09	-.08$	.11	-.10	.17	.01	.12
4	.27*#$	.14	-.02$	.07	-.11#	.15	-.01	.13
8	.22#$	.28	-.06*$	.05	-.13*#	.15	-.03	.09
12	.21*#$	.18	-.06$	.06	-.10#	.17	-.03	.09
16	.29*#$	.19	-.07$	.13	-.16*#	.08	-.05	.12
20	.27*#$	.16	-.22$	.11	-.13#	.14	-.02	.09
24	.29*#$	.16	0$	.05	-.08#	.13	-.02	.07
28	.29*#$	.17	-.06$	.08	-.07#	.15	-.04	.06

Note: * = statistically significant difference compared to pre operative status
= statistically significant difference compared to opposite treatment group
$ = statistically significant difference compared to contralateral joint

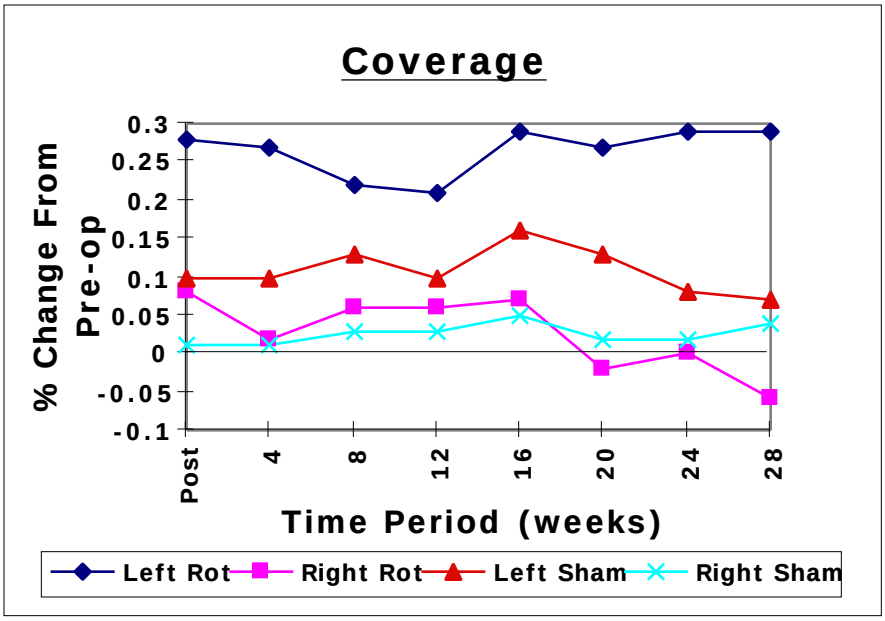


Figure 9: Percentage difference in coverage of the femoral head compared to pre-operatively

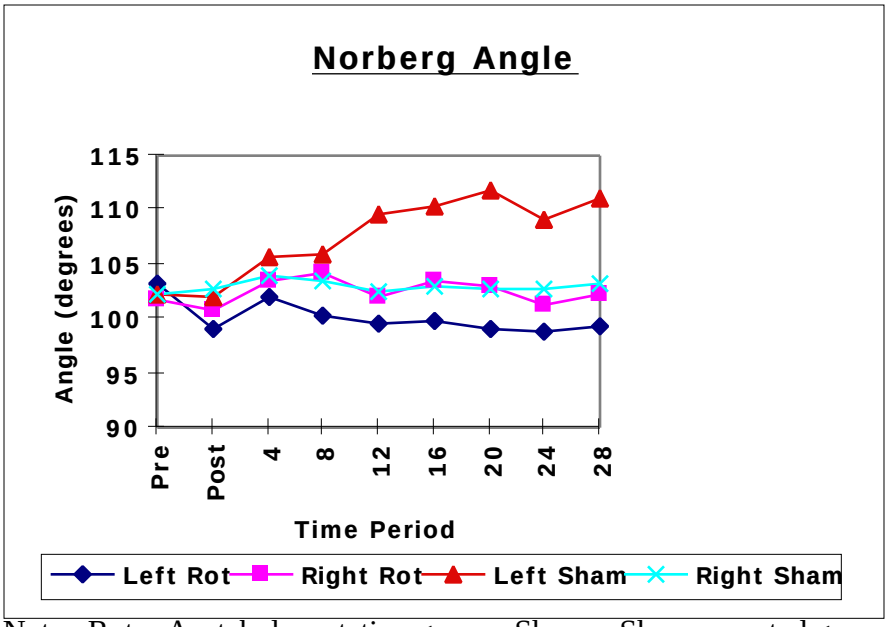
Note: Rot = Acetabular rotation group; Sham = Sham operated group

Similar comparisons were made using Norberg angles (Table 5, Fig. 10). It was found that angles in the rotated hip joints were statistically different from pre-surgical angles immediately postoperatively and at eight, 12, 20, and 24 weeks, but not at four, 16, or 28 weeks. The sham-operated hips were found to be significantly different from preoperatively at two post-operative time periods. Additionally, at four weeks post-operatively, there was a significant difference in the right hip of the sham-operated groupcompared to the pre-operative value. When the Norberg angles were compared between surgery groups, it was found that a statistically significant difference existed in the left hips at all time periods from 12 weeks until the conclusion of the study. On some radiographs the projection of the bone plate obscured the rim of the acetabulum. Estimates of the location of the cranial acetabular edge could not be made, and those radiographs were not evaluated. Due to this, one dog in each treatment group could not have Norberg angles measured. Additionally, five measurements were not made in one dog, and in three dogs there was one radiograph that could not be measured. These changes applied only to the left hip and these data points were eliminated from statistical analysis.

Table 5: Norberg angle

Time Period (weeks)	Rotation Group				Sham Group			
	Left	leg	Right	leg	Left	leg	Right	leg
	mean	STD	mean	STD	mean	STD	mean	STD
Pre-operative	103.33	5.46	101.83	5.32	102.33	3.07	102.17	3.30
Post-operative	99.00 *	1.83	100.80	5.23	101.92	5.44	102.67	3.31
4	102.00	4.90	103.42	5.30	105.60	2.38	104.00 *	2.88
8	100.30 *	3.67	104.10	6.11	106.00	3.92	103.58	3.76
12	99.50 *#	2.92	101.92	6.43	109.63 *#$	3.35	102.5 $	2.30
16	99.70 #	3.46	103.50	5.71	110.38 #$	5.79	102.92 $	2.75
20	99.00 *#	4.70	102.92	8.14	111.90 *#$	4.25	102.83 $	2.58
24	98.80 *#	3.77	101.17	1.63	109.13 #$	4.37	102.67 $	3.61
28	99.40 #	6.13	102.17	3.70	111.00 #$	5.71	103.17 $	4.05

Note: * = statistically significant difference compared to pre operative status
= statistically significant difference compared to opposite treatment group
$ = statistically significant difference compared to contralateral joint



Note: Rot = Acetabular rotation group; Sham = Sham operated group

Figure 10: Norberg angle

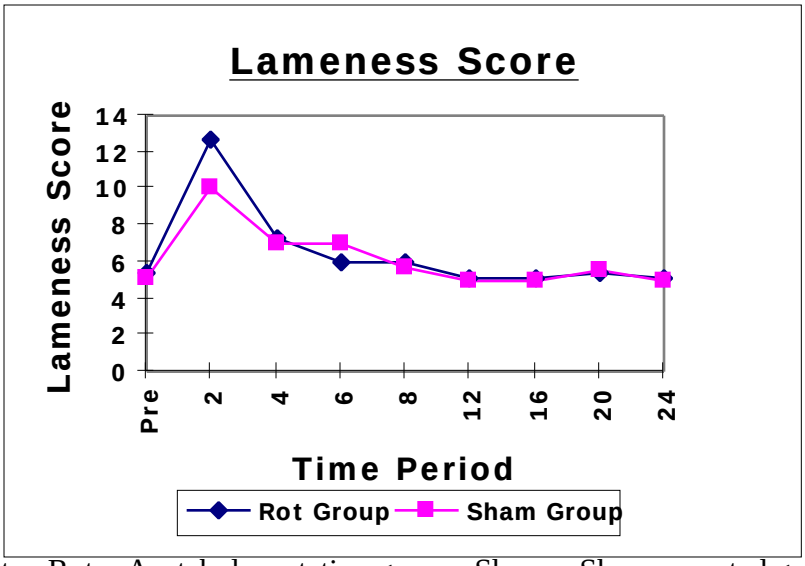
b. Lameness evaluation:

Lameness was evaluated in all dogs and significant differences were noted in all of the lameness scores at two and four weeks post-operatively when compared to the pre-operative scores (Table 6, Fig. 11). At no time, however, was there a significant difference between the two surgery groups.

Table 6: Lameness Scores

Time Period (weeks)	Rotation Group		Sham Group	
	mean	SD	mean	SD
Pre-operative	5.33	0.52	5.17	0.41
2	12.67 *	3.88	10.00 *	2.53
4	7.33 *	0.82	7.00 *	1.79
6	6.00	1.67	7.00	2.76
8	6.00	1.55	5.67	0.52
12	5.17	0.41	5.00	0.00
16	5.17	0.41	5.00	0.00
20	5.33	0.52	5.50	0.55
24	5.17	0.41	5.00	0.00

Note: * = statistically significant difference compared to pre operative status
= statistically significant difference compared to opposite treatment group



Note: Rot = Acetabular rotation group; Sham = Sham operated group

Figure 11: Lameness Scores

Force plate data of vertical forces (Tables 7, 8, Figs. 12, 13), demonstrated statistically significant differences in impulse values from the pre-surgical data for the acetabular rotation limb at all subsequent time periods. The left limb of those dogs undergoing the sham surgery had vertical impulses that differed from pre-surgical during the first three time periods only. Differences were noted in peak force of the left limb for both groups for the first time period, and in the rotated group at the first and second time period. The right limb also had differences at some early time periods. Interestingly, the sham surgery group had peak vertical forces in the right limb that differed from the pre-surgical data on four separate evaluation periods.

When the vertical ground reaction forces were compared between surgery groups, differences were significant for impulse in the left limb from the sixth postoperative week until the conclusion of the study. Values for impulse were not found to be statistically significant when compared between groups.

Braking forces were also evaluated for peak force and impulse (Tables 9, 10, Figs. 14, 15). When the data was compared to preoperative measurements, statistically significant differences were noted at various time periods for all measurements except the impulse in the left limb of the rotated group and the impulse in the right limb of the sham-operated group. The significant changes did not follow any pattern. At no point were differences in braking forces noted between the two surgery groups.

Propulsion forces in the hindlimbs were evaluated in the same manner (Tables 11, 12, Figs. 16, 17). The right limb did not have any statistically significant changes at any time period. The impulse values in the left limb were significantly different from those recorded preoperatively at 2 and 4 weeks for both groups and at 6 weeks for the sham-operated group. Peak forces in the left limb were significantly different from those recorded preoperatively at 2 and 4 weeks for both groups, and at 6 and 8 weeks for the rotated group. At 6 weeks, a significant difference was noted between the impulses for the two surgery groups. No other differences were noted between the two groups.

Table 7: Vertical Ground Reaction Forces

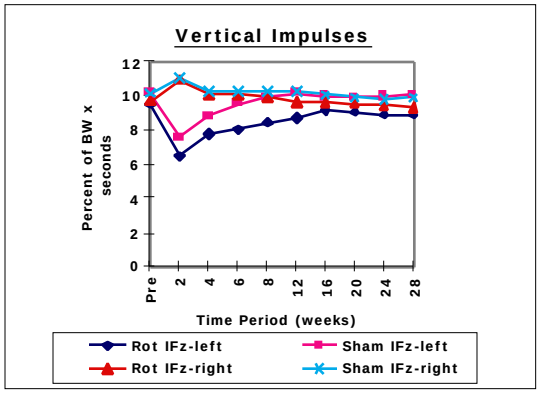
Time Period	Left Limb				Right Limb			
	Rot IFz	Sham IFz	Rot PFz	Sham PFz	Rot IFz	Sham IFz	Rot PFz	Sham PFz
Preop								
2	1	1	1	1	1	1		1
4	1	1	1					1
6	1,2	1,2						
8	1,2	2						1
12	1,2	2						1
16								
20	1,2	2						
24	1,2	2						
28	1,2	2						

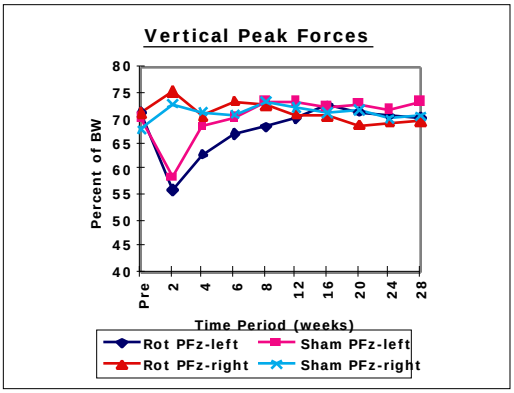
Note: 1 = statistically significant difference compared to pre operative status
2 = statistically significant difference compared to opposite treatment group
3 = statistically significant difference compared to contralateral joint
IFz = Vertical impulse; PFz = Vertical peak force
Rot = Acetabular rotation group; Sham = Sham-operated group

Table 8: Mean Vertical Ground Reaction Forces

Vertical Ground Reaction Forces								
Time Period	Left Limb				Right Limb			
	Rot IFz	Sham IFz	Rot PFz	Sham PFz	Rot IFz	Sham IFz	Rot PFz	Sham PFz
Pre	9.55	10.21	71.19	70.03	9.72	10.18	71.02	67.89
2	6.50	7.61	56.00	58.49	11.02	11.08	75.33	72.91
4	7.75	8.84	63.04	68.33	10.11	10.30	70.56	71.26
6	8.03	9.56	66.73	70.08	10.08	10.26	73.45	70.80
8	8.49	9.92	68.48	73.09	9.93	10.31	72.57	73.44
12	8.81	10.19	70.24	73.24	9.66	10.26	70.85	72.27
16	9.26	10.07	72.56	72.13	9.66	10.15	70.44	70.96
20	9.16	9.96	71.24	72.84	9.57	9.96	68.80	71.75
24	8.99	10.05	70.40	71.72	9.51	9.86	69.20	69.74
28	8.96	10.10	70.17	73.18	9.42	9.94	69.70	70.38

Note: Rot = Acetabular rotation group; Sham = Sham operated group





Note: Rot = Acetabular rotation group; Sham = Sham operated group

Fig 12: Vertical Impulses

Fig 13: Vertical Peak Forces

Table 9: Braking Ground Reaction Forces

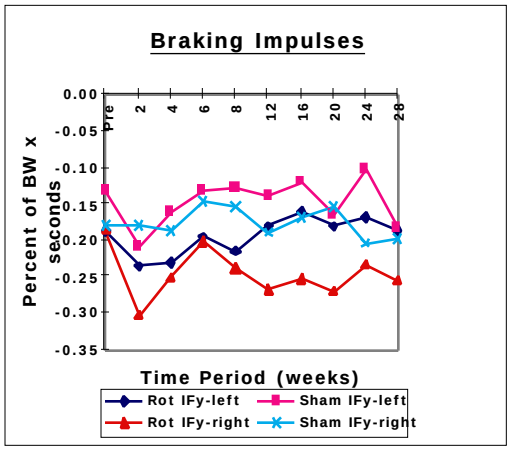
Time Period	Left Limb				Right Limb			
	Rot IFYa	Sham IFYa	Rot PFYa	Sham PFYa	Rot IFYa	Sham IFYa	Rot PFYa	Sham PFYa
Preop								
2		1			1		1	1
4			1	1			1	1
6								
8								1
12							1	1
16					1		1	
20		1						
24					1		1	
28		1		1			1	

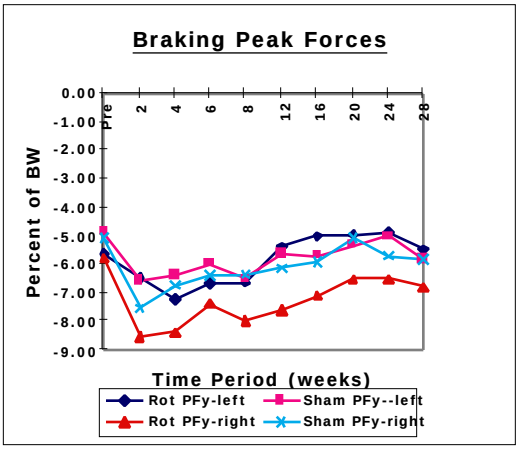
Note: 1 = statistically significant difference compared to pre operative status
2 = statistically significant difference compared to opposite treatment group
3 = statistically significant difference compared to contralateral joint
IFYa = Braking impulse; PFYa = Braking peak force
Rot = Acetabular rotation group; Sham = Sham-operated group

Table 10: Mean Braking Ground Reaction Forces

	Vertical Ground Reaction Forces							
Time Period	Left Limb				Right Limb			
	Rot IFy	Sham IFy	Rot PFy	Sham PFy	Rot IFy	Sham IFy	Rot PFy	Sham PFy
Pre	-0.19	-0.13	-5.62	-4.80	-0.18	-0.18	-5.71	-5.04
2	-0.24	-0.21	-6.43	-6.53	-0.30	-0.18	-8.49	-7.50
4	-0.23	-0.16	-7.20	-6.39	-0.25	-0.19	-8.36	-6.69
6	-0.19	-0.13	-6.65	-5.92	-0.20	-0.15	-7.33	-6.39
8	-0.21	-0.13	-6.57	-6.49	-0.24	-0.15	-7.91	-6.34
12	-0.18	-0.14	-5.35	-5.62	-0.27	-0.19	-7.54	-6.12
16	-0.16	-0.12	-5.00	-5.66	-0.25	-0.17	-7.09	-5.90
20	-0.18	-0.16	-4.94	-5.30	-0.27	-0.15	-6.47	-5.06
24	-0.17	-0.10	-4.82	-4.96	-0.23	-0.20	-6.46	-5.70
28	-0.19	-0.18	-5.46	-5.80	-0.25	-0.20	-6.75	-5.76

Note: Rot = Acetabular rotation group; Sham = Sham operated group





Note: Rot = Acetabular rotation group; Sham = Sham operated group

Fig. 14: Braking Impulses

Fig 15: Braking Peak Forces

Table 11: Propulsion Ground Reaction Forces

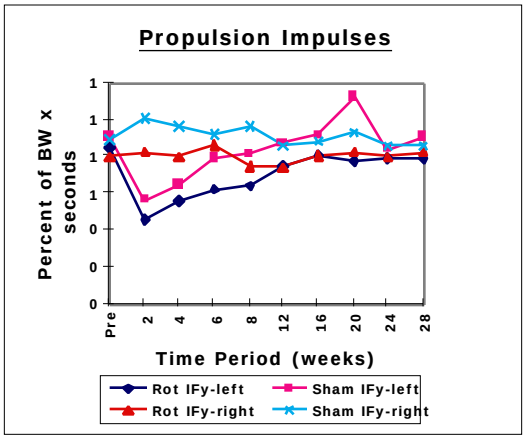
Time Period	Left Limb AR IFYb	Left Limb Sham IFYb	Left Limb AR PFYb	Left Limb Sham PFYb	Right Limb AR IFYb	Right Limb Sham IFYb	Right Limb AR PFYb	Right Limb Sham PFYb
Preop								
2	1	1	1	1				
4	1	1	1	1				
6	2	1,2	1					
8			1					
12								
16								
20								
24								
28								

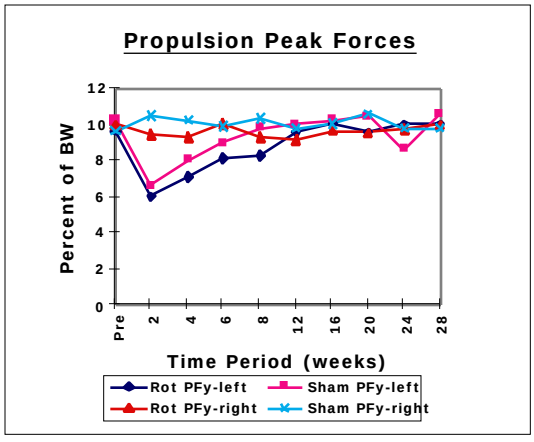
Note: 1 = statistically significant difference compared to pre operative status
2 = statistically significant difference compared to opposite treatment group
3 = statistically significant difference compared to contralateral joint
IFYb = Propulsion impulse; PFYb = Propulsion peak force
AR = Acetabular rotation group; Sham = Sham-operated group

Table 12: Mean Propulsion Ground Reaction Forces

	Propulsion Ground Reaction Forces							
Time Period	Left Limb Rot IFy	Left Limb Sham IFy	Left Limb RotPFy	Left Limb Sham PFy	Right Limb Rot IFy	Right Limb Sham IFy	Right Limb Rot PFy	Right Limb Sham PFy
Pre	0.85	0.91	9.74	10.24	0.80	0.89	10.05	9.73
2	0.46	0.56	6.06	6.63	0.82	1.01	9.52	10.53
4	0.56	0.65	7.13	8.10	0.80	0.97	9.37	10.28
6	0.63	0.79	8.18	9.06	0.86	0.92	10.15	9.94
8	0.64	0.82	8.38	9.85	0.75	0.97	9.38	10.40
12	0.75	0.87	9.63	10.08	0.74	0.86	9.22	9.84
16	0.81	0.92	10.10	10.33	0.81	0.88	9.69	10.13
20	0.78	1.13	9.64	10.45	0.82	0.93	9.60	10.62
24	0.80	0.84	10.02	8.66	0.80	0.86	9.83	9.83
28	0.79	0.91	10.00	10.60	0.83	0.86	10.05	9.87

Note: Rot = Acetabular rotation group; Sham = Sham operated group





Note: Rot = Acetabular rotation group; Sham = Sham operated group

Fig 16: Propulsion Impulses

Fig 17: Propulsion Peak Forces

c. Necropsy findings:

Disarticulation and examination of the left and right coxofemoral joints (Fig. 18-21) was performed, but not statistically analyzed. In no cases were severe erosions or osteophytes present. In some hips, thinning and yellowing of the cartilage was observed. There was occasional slight flattening of the femoral head. These findings did not correlate with which surgery had been performed.

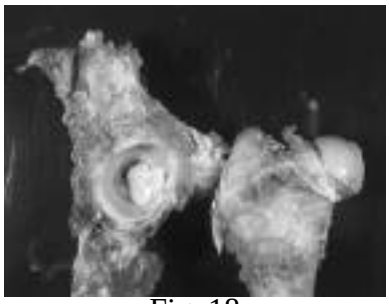


Fig. 18

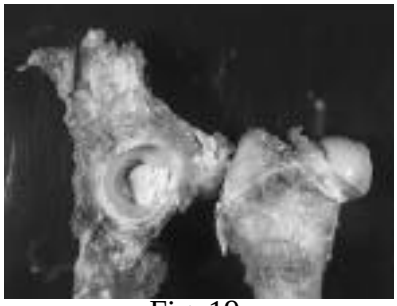


Fig. 19

Fig. 18, 19: Gross findings from sham operated dogs showing a normal hip (Fig 18) and cartilage (Fig. 19).

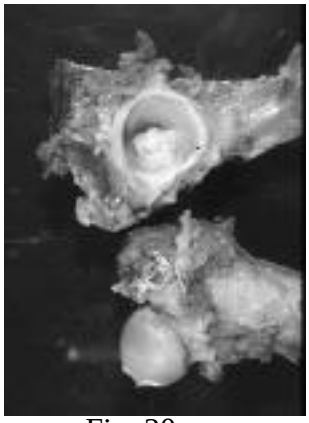


Fig. 20

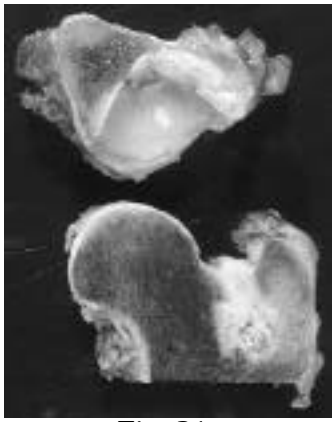


Fig. 21

Fig. 20, 21: Gross evidence of osteoarthritic change from a dog in the acetabular roation group showing discoloration of the femoral head (Fig 20) and thinning of the cartilage with altered shape of the femoral head (Fig.21).

d. Histologic evaluation:

Histologic evaluation of the articular cartilage demonstrated a wide range of lesion severity. Several samples showed no change, and some demonstrated obvious arthritis. More severe lesions included fissures in the cartilage, superficial cellular disruption and mild clustering, as well as decreased stain uptake (Fig. 22, 23). At no point was tidemark integrity compromised. Several dogs showed mild changes in the unoperated hip, and one dog in the acetabular rotation group showed more severe change in that hip than the operated side. The sham-operated group occasionally had scores consistent with moderate

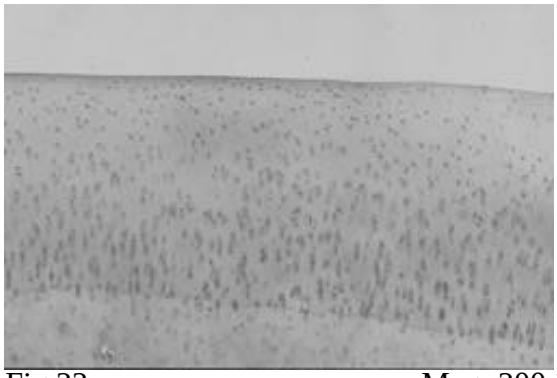


Fig 22 Mag=200x

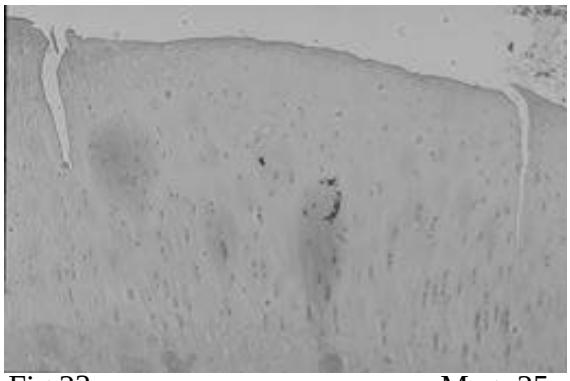


Fig.23 Mag=25x

Fig. 22, 23: Histologic samples of cartlage from a sham-operated dog (Fig. 22) showing normal cartilage from an acetabular rotation dog (Fig 23) showing osteoarthritic change.

change. When the histologic scoring was evaluated between treatment groups and between left and right legs, no statistically significant differences were found (Table 13). In some joints, the ligament of the femoral head was hypertrophied, but this was difficult to quantify and was not scored for analysis.

Table 13: Histologic scores

	Rotation group		Sham group	
	Left	Right	Left	Right
Cartilage mean	3.67	2.17	3.00	1.67
st. dev.	2.50	2.64	2.81	1.03
Capsule mean	0.97	0.42	0.83	0.50
st. dev.	0.33	0.38	0.82	0.77

A range of lesions was present in the histologic evaluation of the joint capsules (Fig. 24, 25). A statistically significant difference was present when the severity of lesions was compared between the right and left legs of the treatment group. There was no statistically significant difference between surgery groups.

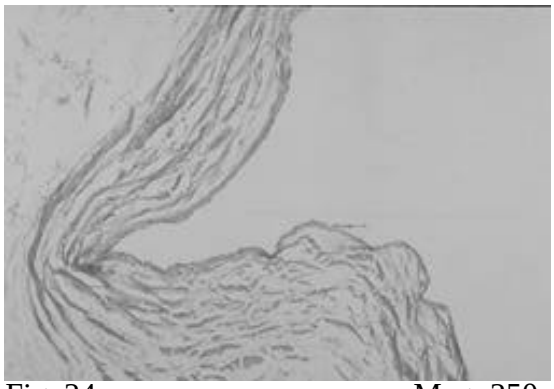


Fig. 24 Mag=250x

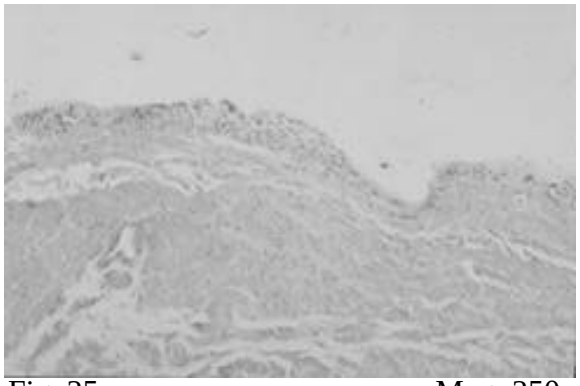


Fig. 25 Mag=250x

Fig. 24, 25: Histologic samples of joint capsule from a sham-operated dog (Fig. 24) showing normal joint capsule, and from an acetabular rotation dog (Fig 25) showing hypertophy.

Discussion

In the original description of this experimental model, radiographs were taken at varying time intervals and only one example was used to show decreased coverage of the femoral head by the acetabulum.[112] This finding was not quantified, nor were descriptions of other radiographic changes included. After seven months, the dogs in the current study did not show radiographic evidence of OA. This reflects the apparently mild nature of the degenerative process created. Given that gross and histologic lesions were present, radiographically detectable changes would likely appear with time.

In the only other surgical model of coxofemoral OA, the radiographic signs of joint disease were not well described.[76] It was noted that the femoral heads were subluxated, but not whether osteophytes were present. At necropsy, gross evidence of hip dysplasia was reported, but not clearly described. Furthermore, the procedure was performed in immature dogs, which limits the comparison to the current investigation, and the control hips had gross evidence of spontaneous hip dysplasia. It was not known prior to this investigation how soon and to what extent radiographic evidence of degenerative joint disease would occur.

Assessment of coverage of the femoral head by digitized scanning was listed as the percentage change from pre-operative values. The value at each time period was subtracted from the pre-operative value and this difference divided by the pre-operative value. The resulting percentage change was thus negative if the amount of coverage had increased, and positive if the coverage had decreased. Analysis of data showed that at many time periods following surgery the left hip of the rotated group had significantly decreased coverage compared to preoperative values and compared to the opposite surgery group. A difference between right and left hip joints was noted in the acetabular rotation group. Analysis of the data suggests that the difference between surgery groups resulted mainly from the change in the sham-operated dogs. These hips did not show statistical difference from the contralateral joint due to high standard deviations. The difference compared to pre-operative levels in the operated hips of the acetabular rotation group may suggest that some laxity, and therefore subluxation, was developing despite the fact that none was ever palpable nor was subluxation noted on the hip-extended views. It should be noted that the acetabulae were rotated around an axis roughly parallel to the midline of the ilium and the point of reference on the acetabular rim may or may not have changed. This could have caused some of the difference compared to pre-operative values and given a false impression of subluxation. The consistency of the values in the sham operated dogs over the course of the study is evidence that the method used was reliably repeatable

As noted earlier, Norberg angle is a method used to evaluate hip subluxation. In general, larger numbers are associated with tighter hips, although the ultimate correlation with the development of degenerative joint disease has been questioned.[53] The values recorded for this measure tended to have a high standard deviation which influenced statistical differences. The difference between surgery groups in the left hip confirmed the effect of surgical manipulation. Because this change occurred immediately post-operatively, it cannot be attributed to joint capsule or ligament stretching which would occur over time. Additionally, since the dogs in this investigation were mature, it was less likely that the joint capsules and ligaments would stretch and allow significant subluxation. This is in contrast to the situation in CHD in young dogs in which the tissues do stretch for a period during growth, thereby allowing subluxation to occur.

Subjective evaluation of the degree of lameness did not show a difference between the surgery groups. This is not surprising given that the dogs in both groups seemed normal by the third or fourth evaluation period post-operatively . The arthritic change seen on histopathologic evaluation was apparently mild enough and occurred late enough in the study to not cause an appreciable degree of discomfort. The lameness examination findings correlated with data obtained from the forceplate evaluations. In their work, Inerot *et al* noted that the dogs were non-weight bearing for one to two days, and had a slight limp for 2-4 weeks.[112]

Forceplate findings were consistent with dogs recovering from surgical trauma. Dogs in both treatment groups were noticeably lame during forceplate evaluation at the first two time periods. Ground reaction force data generally supported this impression. After the early evaluation times, changes were less frequently seen in control animals. Some of the observations that demonstrated statistically significant changes in the right leg or at late time periods are unlikely to be due to the model and may represent variance in the animals gait. These inconsistent findings are most frequent in the data for braking forces, which may not be as important.[134]

The consistent post-surgical change in the vertical impulses suggests some degree of lameness. The impulse value involves both the force generated by the limb and the time that the paw is in contact with the ground; it therefore may provide more information than the peak force. Since this finding was not true in the peak forces as well, we can assume that the change was due to the length of time the dogs kept the paw in contact with the ground. This is not a fuction of mechanical disability, but of pain, and represents a very subtle lameness. The lameness detected is consistent with the early stages of disease, and may be useful in testing the effect of intervention in those situations.

Some of the earliest gross pathologic changes occurring in canine hip OA include a loss of normal shine to the cartilage, and a dull yellow or gray appearance in focal areas.[5] Other changes that occur early in the disease are thickening of the joint capsule and ligament of the femoral head.[5,25,26] Sections for histopathologic evaluation were cut to include the ligament, although the changes were not quantified. The mild changes in the cartilage initially can progress to erosions,[26] and all of these changes were seen to some extent in the dogs of this study.

The Mankin histologic grading scale for OA was first proposed in 1971, and the scale has been used extensively since that time.[135] It evaluates histologic sections according to the four categories of structure, cell abnormalities, stain uptake, and tidemark integrity. A score of zero indicates normal cartilage, while a score of 14 would indicate the maximum expression of arthritic change. Recently, the reliability of the Mankin score was evaluated, and a modified system was found to be more consistent.[131] Differences in the new score include the elimination of evaluation of the tidemark and better definition of categories. The modified scoring system was chosen because of its higher reliability and more precise category definitions

Inerot *et al* described a variety of histologic findings in dogs following acetabular rotation.[136] In some dogs, small samples of cartilage were obtained and stained with hematoxylin and eosin, toluidine blue, and alcian-periodic acid-Schiff. A loss of stainability was noted in one specimen obtained ten days post-operatively. In one dog killed 19 days post-operatively, no histologic lesions were noted. At 67 days post-operatively, necrotic cartilage and pannus formation were found in a third dog. Quantification of the histologic findings was not attempted. Larger sections of the femoral head were taken from two dogs killed at 119 and 153 days, respectively. Changes in these specimens ranged from loss of stain uptake and chondrocyte clustering to deep erosions

and subchondral bone atrophy. No macroscopic changes were seen in the cartilage on the non-operated side, nor was synovitis observed.

Because or variations in sample sizes and times, and the lack of quantitative scoring of the histologic lesions in the report by Inerot *et al* direct comparison between that study and the current investigation is difficult. Decrease in stain uptake, and occasional clustering of chondrocytes was observed in the dogs in our study . Only mild disruption of cartilage architecture was seen, although some fissures were present. These findings appear similar to those described by Inerot *et al.* The dogs in the current investigation microscopically had a mild synovitis which was described in the original study. Although synovitis is produced in the Pond-Nuki model, we did not expect a significant synovitis in this acetabular rotation model as it is not reported to occur in other models where the joint capsule is not opened.[107] Some degree of synovitis is a component of the naturally occurring disease, however. The cause of the synovitis in our dogs is likely related, in part, to the stretching of the joint capsule following the application of the twisted plate. The regional musculature and the joint capsule may have been subjected to greater forces to keep the joint reduced, which in turn caused an inflammatory response. Some of the dogs in the sham operated group had a synovitis which may have been related to undetected underlying laxity. Alternatively, the synovitis in those dogs may have been related to inflammation resulting from surgical disruption or from regional tissue healing, although this would have been expected to cause change in all the operated hips. We do not feel that the blood supply to the joint capsule or the subchondral bone was disrupted by the surgical manipulation. In none of the dogs were the synovial changes severe.

Several possible explanations for the failure of this model to produce severe OA exist, the most plausible being that the alterations to joint biomechanics that were created were mild, and any laxity that developed was insignificant, therefore arthritic changes were slow to develop. Many dogs with naturally occurring hip dysplasia do not show radiographic evidence of OA until after two years of age.[53] Most clinically affected dogs show clinical signs of pain and joint laxity between 4 months to 1 year of age, and radiographic changes do not appear until after 6 months of age.[40] In dogs with severe disease, radiographic changes are not extremely obvious until after two months of age.[26] Given that the dogs in our study were adult and biomechanical alterations were not substantial, it is not surprising that they did not to develop severe radiographic changes.

In comparison to the typical lesions seen in the Pond-Nuki model, the current model showed milder disease. One significant difference is that the model investigated here does not involve an arthrotomy, which can cause an inflammation that may contribute to the progression of disease. In only one of the rotated hips in our study was the synovitis considered moderate, with the changes in the remaining joints absent or mild. Because the dogs in the current study did not undergo arthrotomies and showed evidence of arthritic changes in the cartilage, this model may produce mild OA that more closely mimics the natural disease. Naturally occurring OA is slow in onset, and progresses over years; were these dogs examined after more time had elapsed, it is likely that the arthritic changes in the hip joints would have become more substantial.

The amount of rotation provided by the bone plates applied to the acetabular rotation group might not have resulted in a sufficient biomechanical force to cause mechanical trauma to the joint and might have limited the severity and speed of onset of the OA in this study. It would seem, however, that the 45 degrees of rotation used would cause a substantial change. Clinical experience during triple pelvic osteotomy surgery has shown that excessive rotation of the acetabulum can cause interference between the acetabulum and the femur when the pelvis is rotated in the typical manner. Additional rotation in this study could have caused a similar situation, and would have required the use of straight plates

bent by hand. The pre-twisted plates were chosen for this experiment because we felt that a greater degree of standardization between dogs could be achieved in that manner, and because, although no direct comparison has been made to the author's knowledge, hand bending a plate may cause it to be weaker and consequently some of the twist applied could be lost. The degree of rotation achieved in our model was likely greater than that achieved by Inerot *et al.* In their model, the pubis was not cut, and the caudal aspect of the ilium was placed medial to the cranial portion via a stepped cut.[112] This is similar but opposite to the original description of triple pelvic osteotomies in dogs.[137] One technique has been described for evaluation of the degree of axial rotation achieved with triple pelvic osteotomies, but it is performed in vitro and therefore was not used in this investigation.[138]

Another explanation for the milder arthritic change seen in this study compared to the original model may relate to the age and weight of the dogs. The dogs used in this investigation were of unknown age, but were judged to be adult based on physical and radiographic examinations. Inerot *et al* used dogs between the ages of 12 and 18 months, which may have had more pliable joint structures and remaining growth, and could have been more susceptible to the effects of altered joint conformation. The greater elasticity of the joint capsule and ligament might have allowed laxity to develop more easily. Although the weights of the dogs in the investigation by Inerot *et al* were not described, all were either greyhounds or pointers. The dogs in the present study all weighed more than 27 kg and may have been smaller than those in the first investigation and consequently less susceptible to the arthritic change. The dogs in our investigation varied in weight, however, and no correlation was noted between weight and the development of arthritic lesions.

It is important to note that all evaluation methods have a lower limit of sensitivity, and this impacts investigators' ability to detect subtle changes. One way to better investigate and compare the OA in this model may be to use more sensitive methods of evaluation. MRI has been used to study cartilage structure. Cartilage changes are detectable through this modality, although it is somewhat expensive and not readily available.[103]

The appearance of Mankin Scores suggestive of OA in two of the sham-operated dogs and one of the non-operated hips of a dog in the rotated group is difficult to explain. Although the anatomic alignment of the bone fragments in the sham-operated dogs may not have been anatomic, it was obviously better than in dogs in which the twisted plates were applied. It is possible that those dogs had mild degrees of underlying OA in their hip joints which were not detected on physical or radiographic examination. Large mixed-breed dogs, have a high incidence of hip dysplasia. The use of a breed with a very low incidence of hip dysplasia, e.g. greyhounds would have been desirable but this was not possible because of availability and cost.

This investigation supports the findings of Inerot *et al* that this experimental model causes the development of osteoarthritis, but the changes are subtle and slow to develop. The model does not, however, lend itself to evaluation using the assessment methods described in this study. Lameness or radiographic change are assessed to evaluate the efficacy of medical or surgical treatments. The dogs in this study did not show these signs, so it would not be possible to use them to measure treatment response within the period of time over which these dogs were evaluated. Biochemical and histological data could be obtained post-mortem, but this is not always desirable. An additional difficulty in applying this model to many research studies is that the changes occurred late in the study. It is sometimes impractical for reasons of finance and time constraints for researchers to use a protocol necessitating greater than seven months of investigation.

Given that histologic changes were noted, and OA is a progressive disease, a longer study period may have yielded more severe arthritic lesions. The histologic findings confirm that arthritic degeneration was occurring, but the *in vivo* methods of evaluation were unable to detect change. Radiographic evidence of OA appears after the onset of pathologic lesions. Lameness evaluations also have a lower limit of sensitivity. In order to use this model, it would be necessary to study mild early changes of OA. Its use in the study of more severe forms of OA would require observing the dogs for a longer period of time.

Conclusions

The model for experimentally-induced osteoarthritis in the canine hip joint evaluated in this investigation resulted in the development of mild arthritic change in many joints of the acetabular rotation group. Only minimal or no change was seen radiographically and on subjective evaluation of lameness . These results suggest that the model does cause mild OA which would likely become more severe with longer periods of time. As a research tool, the model may mimic naturally occurring osteoarthritis. More sensitive evaluation techniques than those used in this study would be necessary to fully utilize this model in OA research.

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