REVIEW

Animal models for osteoarthritis: processes, problems and prospects

Kenneth P H Pritzker

Model systems are systems that are used to simplify complex phenomena and to understand otherwise elusive processes.¹ An animal model for human disease can be defined as a homogenous set of animals which have an inherited, naturally acquired, or experimentally induced biological process, amenable to scientific investigation, that in one or more respects resembles the disease in humans.^{2 3}

Elusive and complex as a precise understanding may be, virtually all definitions of osteoarthritis express the disease as transient and progressive structural changes in joint tissues, principally articular cartilage, subchondral bone, synovium, and synovial fluid.^{4 5} Articular cartilage oedema, fibrillation, and erosion accompanied by chondrocyte proliferation and decreased staining of matrix proteoglycans, subchondral bone thickening, deformation of the articular surface, osteophyte formation, synovial intimal cell hyperplasia, and synovial fibrosis are some of the standard features associated with osteoarthritis. These changes result from a poorly understood but very large series of functional events which may occur over a large fraction of the life of each affected individual. Biochemical, cell or organ culture models can provide information and insight concerning the mechanisms for functional events within cartilage, bone or synovium or selected cells within these tissues. These *ex vivo* models, inherently more highly controlled than animal models, are most useful for understanding short term biological events, and events isolated from the physiological influences of adjacent structures and general metabolism. As yet, *ex vivo* models cannot simulate the structural changes which occur in joint tissues in animals over months to years. Hence, animal models for osteoarthritis are required to study how the complex structural changes in tissues evolve over time, spontaneously or following experimental injury, and to determine how constitutive, environmental or biomechanical risk factors⁴ may initiate, promote, or otherwise regulate these changes (table 1). Animal models are also needed to show how therapeutic strategies may ameliorate, resolve or prevent osteoarthritis.^{6–8}

The decision to use a particular animal model to study osteoarthritis is governed by criteria of relevance, appropriateness, and availability.^{3 9 10} Relevance refers to the comparability of the phenomenon studied in animals to the corresponding process in human disease. Animals with characteristics similar to

Table 1 Osteoarthritis: constitutional and environmental factors

Constitutional factors
• Genetics
• Age
• Sex, Parity
• Hormone and metabolic factors
• Social rank
Environmental factors
• Nutrition
• Exercise
• Drugs
Biomechanical forces
• Joint instability
• Displaced joint loads
• Joint overloading

human disease as well as animals with features that differ in a known specific manner from human osteoarthritis may provide relevant models. Appropriateness refers first to the need to use animals rather than simpler models to investigate the process in question and second to the specific criteria that make one set of animals more appropriate than others for the experimental goals and objectives. Simplicity, predictability in reproducing circumscribed aspects of the disease, as well as the capacity to induce new insight, are appropriate factors when animal models are considered.⁹ For example, to test drug effects on an animal model, simplicity and predictability are paramount whereas to understand pathogenesis, a more complex model that more closely mimics human disease may be more appropriate. Availability criteria refers to practical factors such as adequacy of animal supply, the presence of controls, the ease of handling and environmental maintenance, as well as costs (table 2).

Table 2 Animal models for osteoarthritis: availability criteria

• Genetic homogeneity or heterogeneity
• Availability and homogeneity of nutrition and exercise history
• Life span of animal, time span of disease, age of onset
• Disease frequency
• Availability of matched control population
• Anatomical and physiological attributes
Quantitative
• Joint tissues sufficient for studies
• Adequate access to synovial fluid
Qualitative
• Resemblance to human tissues
• Weight bearing vs non weight bearing joints
• Availability of experimental techniques for model
• Supply of animals—standardisation
• Ease of handling
• Access of model to experimental manipulation
• Drugs
• Physical intervention
• Previous research in model (background knowledge, peer acceptance)
• Costs

Connective Tissue
Research Group,
Mount Sinai Hospital,
Toronto, and
Departments of
Pathology and
Surgery,
University of Toronto,
Toronto, Canada
K P H Pritzker

Correspondence to:
Dr K P H Pritzker,
Department of Pathology,
Mount Sinai Hospital,
600 University Avenue,
Toronto, Ontario,
Canada M5G 1X5

Table 3 Development of animal models for osteoarthritis

1	Disease identification or induction in a set of animals
2	Availability of sufficient animals under experimentally controlled conditions
3	Characterisation of functional and structural similarities and differences between the model and human osteoarthritis
4	Testing hypotheses related to osteoarthritis aetiology, pathogenesis or therapy

There are several stages in the development of animal models for osteoarthritis (table 3). Firstly, the disease is identified or induced in a set of animals. With spontaneous disease, this may result from incidental comparative pathology observations or more rarely as with primate CPPD crystal arthropathy, from a deliberate search for the disease.^{11–13} Secondly, availability criteria must be considered. Animal models requiring colonies of large animals such as dogs or primates are available only within special facilities. Thirdly, the biological similarities and differences between the model and human disease must be demonstrated. Finally, when the model is well characterised, features of the model become useful to test hypotheses related to the pathogenesis or therapy of osteoarthritis.

Controlled investigation of structural changes in human osteoarthritic joints has severe limitations.^{10 14 15} Humans with osteoarthritis have extensive genetic heterogeneity, and a varied nutritional, biomechanical, and pharmacological history, all of which can be only incompletely ascertained by epidemiological methods. Further, the lack of precise non-invasive methods to identify early disease, the relative inaccessibility of diseased tissues for sampling and even greater limitations in obtaining control tissues are obstacles to using human tissues for the study of osteoarthritis.¹⁶ This implies that to model the changes in joint organisation in osteoarthritis experimentally, a holistic system analogous to humans, namely animal models, is required.

Conceptually, by simulating osteoarthritic structural changes, animal models can demonstrate the sequence and specificity of each identified structural feature. By correlating the structural changes with putative systemic biological factors, the association of each factor with each change can be assessed. By manipulating the animal model pharmacologically or

physically, factors that regulate the onset, progression, or control of osteoarthritis may be identified.

Although osteoarthritis affects other joints such as the intervertebral discs of the spine as well as synovial joints, models for spinal osteoarthrosis are beyond the scope of this review.

This paper discusses the types of animal models that have been used to study osteoarthritis affecting synovial joints, the features, advantages and disadvantages of each class of models, and the insights into an aetiopathogenesis that may be obtained from the study of selected animal models. The reports cited emphasise the advances of the past decade. For previous work see reviews by Gardner,¹⁷ Bentley,¹⁸ Arlet and Gédéon,¹⁹ Troyer,¹⁴ Adams and Billingham,¹⁵ Moskowicz^{20 21} and more recently Altman and Dean.¹⁰

Classes of osteoarthritis animal models

Osteoarthritis models can be classified into two major groups, experimentally induced models and spontaneous disease models (table 4). On the basis of pathogenesis, Arlet and Gédéon divided experimentally induced osteoarthritis into two categories, mechanical arthrosis and structural arthrosis.¹⁹ Mechanical arthroses are induced by altering the amount and distribution of biomechanical forces on otherwise normal joint tissues. Structural arthroses are induced by physical, chemical, endocrine, biochemical or immunological alteration of one or more joint tissues. In this review, to emphasise the degenerative or non-inflammatory features, we will continue to use the term arthrosis to denote each class of model disease. To conform to current terminology, each particular model will be referred to as *arthriti*s. To emphasise the role of the biological reaction to injury in the pathogenesis of mechanically induced models, we will refer to these models as *biomechanical* models. As described below, the concept of experimentally induced biomechanical and structural arthroses can be extended from monoarticular arthroses to include polyarticular models. As expected, spontaneous disease models are exclusively models of polyarticular disease (table 4).

Table 4 Animal models for osteoarthritis

	Monoarticular	Polyarticular
<i>I Experimentally induced arthroses</i>		
1 Biomechanical arthroses		
Destabilisation models	•	
Displaced biomechanical load models	•	
Repetitive overload models	•	•
2 Structural arthroses		
Surgical injury, for example, incision, excision	•	
Trauma, for example, abrasion, contusion	•	•
Physical	•	
Chemical	•	
Enzyme and cytokine activity	•	
Drugs	•	•
Nutrition		•
Post inflammatory	•	•
(Transgenic animals) (?)		•
<i>II Spontaneous arthroses</i>		
Spontaneous degenerative arthritis (feral and wild animals)		•
laboratory bred species		•
Osteological and paleontological tissue human and other species	•	•

Experimental monoarticular osteoarthritis models

As described in previous reviews, all experimentally induced monoarticular osteoarthritis models are essentially joint injury and repair models^{10 14 15 17–21} (tables 5, 6). Common features of these models include the ability to define precisely the type of injury, the severity of injury as well as the time of onset and progression and to relate these events to markers of disease activity. Appropriate controls are readily available in the contralateral joint. However, as even local lesions may have systemic or biomechanical effects in the contralateral limb, controls from joints of age matched animals are preferred. The principal limitation of these models is that the experimental injury is induced over a short time

Table 5 Experimental biomechanical arthroses

Monoarticular arthroses	
1	Destabilisation models
	<ul style="list-style-type: none"> ● Patellectomy and patellar dislocation ● Ligament transection ● Meniscectomy $\pm$ ligament transection ● Tendonotomy and myectomy ● Denervation
2	Displaced biomechanical load models
	<ul style="list-style-type: none"> ● Osteotomy ● Compression/immobilisation ● Immobilisation
3	Joint overloading—chronic repetitive
	—acute
Polyarticular arthroses	
	<ul style="list-style-type: none"> ● Overloading joints on hard surfaces ● Overloading of immature joints

and is superimposed rapidly on normal joint structure at the age of the animal studied. These models are therefore particularly useful for understanding responses of joint tissues to specific injuries as well as for simulating the onset and evolution of secondary monoarticular osteoarthritis.

Monoarticular biomechanical arthrosis

Monoarticular biomechanical arthroses are of two types: joint instability models and displaced biomechanical load models (table 5). The first joint instability models were induced by patella dislocation²² and patellectomy.²³ These procedures in which extensive surgical disruption of the joint produced joint instability led rapidly to severe erosive and proliferative lesions of all joint tissues.

To study the development of lesions, joint instability models producing less severe injury and more gradual progression of degenerative changes were required. The first joint instability models meeting these criteria were established by Pond and Nuki²⁴ who refined

the canine knee joint anterior cruciate ligament transection model of Paatsama²⁵ and by Moskowitz *et al* who developed the partial meniscectomy model in rabbits.²⁶ Both models were stimulated by clinical observations that joint instability could lead to progressive degenerative arthritis. These models, their variants and successors initially produced joint inflammation and repair, particularly in cartilage and synovium.^{27–29} With continuing instability, erosive and proliferative changes in cartilage and subchondral bone developed that resembled changes in spontaneous osteoarthritis.^{27–30–35} Although much more expensive, the advantages of the canine and sheep models over smaller animals include the increased amount of cartilage available for biochemical analysis, cell biology investigation,^{10–33–36–46} biomechanical studies^{47–48} and the ability to study long term changes in these animals with non invasive methods such as magnetic resonance imaging.^{33–35} Conversely, joint instability arthrosis in the rabbit and other small animal models may be more useful where large numbers of animals are required to study the effects of pharmacological agents such as oestrogen^{49–50} or glycosaminoglycan compounds^{51–52} on the regression of degenerative osteoarthritis. Particular variants have special applications. For example, as guinea pigs require exogenous vitamin C, the effects of vitamin C depletion and repletion can be studied by inducing joint instability lesions in this animal model.^{53–54} Immobilisation following intra-articular instability injury protects against development of degenerative arthritis.^{55–56} This demonstrates that joint instability coupled to shifting of normal loads can induce progressive lesions with features such as cartilage fibrillation, erosion, chondrocyte proliferation and marginal osteophyte formation that are similar to human osteoarthritis. With the intra-articular surgical instability models, there is evidence that the traumatic injury associated with the surgical procedure itself and the presence of haemarthrosis advances the development and extent of early lesions, in particular, synovitis.^{57–58}

In long term studies, haemodynamic and tissue diffusion compromise by synovial pathology may interfere with nutrition and metabolite clearance thereby promoting further articular degeneration.⁵⁹ Bole and colleagues have shown that joint instability induced by the extra-articular procedures of myomectomy and tendonotomy can produce progressive degenerative changes in guinea pig cartilage and subchondral bone.^{60–61} Sensory denervation in itself does not appear to induce degenerative arthritis. Denervation does accelerate degeneration in the canine anterior cruciate ligament transection model.⁶² Corticosteroid therapy, by reducing the proliferative activity of synovial cells, chondrocytes and bone cells, can reduce the severity of joint lesions induced by anterior cruciate ligament transection.⁶³

Displaced biomechanical load models are models in which degenerative changes in joints are induced by altering load distribution

Table 6 Experimental monoarticular structural arthroses

I Extracellular matrix directed	
Physical	
	Surgical trauma: incision, abrasion, contusion, defects
	heat
	laser energy
Chemical	
	Acids, alkalis
	Protein denaturants, for example, formaldehyde
	Water and ionic solutions, for example, saline
Enzymes	
	Papain
	Trypsin
	Hyaluronidase
	Collagenase
II Articular cell directed	
Physical	
	Freezing
	Electrolysis
	Ionising radiation
Chemical	
	Osmic acid
	Thiotepea, colchicine, nitrogen mustard
	Iodoacetate
	Polyene antibiotics, for example, filipin
	Vitamin A
Hormones, cytokines and other mediators	
	Hormones, for example, growth hormone, cortisone
Intra-articular inflammation	
Non-infectious	
	Papain
	Zymosan
	Carrageenin
	Tissue fragments, for example, cartilage, fat
	Crystals
	Infectious, for example, bacteria
Specific cytokines	
	Interleukin-1
	Tumour necrosis factor
	Transforming growth factor— β 2

without decreasing biomechanical stability. Osteotomy, compression and immobilisation are examples of procedures which can redistribute joint loads. Tibial osteotomy imitating valgus deformity has been used in rabbits⁶⁴ and dogs.^{65–66} Histologically and biochemically the lesions appear much milder than instability lesions but do involve areas of both increased and decreased joint loading. In contrast, in studies by the same investigators, pelvic osteotomy produced more extensive degenerative changes in cartilage than anterior cruciate ligament transection.⁶⁷ These studies indicate that under normal biomechanical conditions, joint tissues can adapt over time to mild and moderate shifts in ambient load distribution. Conversely, acute changes of load distribution may have deleterious effects in joint tissues subject both to decreased and increased loading.

Compression/immobilisation models of degenerative osteoarthritis were derived from studies of the previous orthopaedic practice in which joints were immobilised in forced fixed positions.⁶⁸ With compression/immobilisation, excessive pressure and/or interference with synovial fluid flow induces chondrocyte necrosis and cartilage erosion, as well as proliferative changes in the adjoining less compressed cartilage.^{56–69–71} These studies led to the recognition of the importance of joint motion to joint healing and to the development by Salter of continuous passive motion as a chondroprotective therapeutic modality.^{72–73}

With pure immobilisation models, early events include synovial effusion with the presence of neutrophils.⁷⁴ Subsequently, cartilage proteoglycan depletion with increased ³⁵SO₄ uptake is observed indicating that proteoglycan synthesis is increased.^{71–75–77} Prolonged immobilisation, even if interrupted by periods of mobility results in progressive cartilage lesions such as matrix fibrillation and erosion.^{71–76–78} Administration of exogenous growth hormone does not prevent the degenerative lesions but does accelerate restoration of cartilage integrity following remobilisation.⁷⁹ In the dog, immobilisation leads to proteoglycan depletion that involves the contralateral joint indicating that systemic factors, such as decreased exercise, may be partly responsible for the changes rather than immobilisation itself.⁸⁰ These lesions are more severe with concomitant aspirin therapy.⁸¹ Prolonged immobilisation leads to cartilage erosion and extensive regional osteopenia.⁷¹ Remobilisation tends to limit and reverse the adverse effects of immobilisation.^{78–82–83} Treadmill running exercise does not affect articular cartilage morphology in normal animals. Excessive exercise, however, following remobilisation accelerates the degenerative lesions in cartilage.^{74–83}

More recent models have demonstrated degenerative articular changes with excessive forces both after repetitive axial joint overload in the presence of joint motion^{84–87} and after a known acute transarticular load.⁸⁸ Rabbit joints subjected to passive motion and overloading develop degenerative, proliferative

and remodelling changes in both cartilage and subchondral bone.⁸⁵ Cartilage fibrillation, erosion, as well as articular plate remodelling can be induced in dog patellae six months after the application of an acute transarticular load to the knee joint sufficient to fracture the uncalcified cartilage and subchondral bone but leaving the calcified articular cartilage intact.⁸⁸

Polyarticular biomechanical arthroses

The anecdotal wisdom of livestock owners states that to prevent degenerative arthritis, horses should not be raced until the age of two years, and cow barns should have earth rather than concrete floors.⁸⁹ Both ideas are rooted in the concept that repetitive impact loads should not exceed the capacity of articular skeletal tissues to dissipate the absorbed energy stored between each stress. Drawing from this folklore and from mechanical engineering principles, Radin and his colleagues studied scientifically the effects of repeated impact loads on the development of osteoarthritis.^{84–86–87–90–91} Using sheep as a model, Radin induced articular cartilage and subchondral bone degenerative changes in animals exercised on hard concrete surfaces compared with control animals exercised on softer wood chip paths.⁹⁰ Although multiple joints are involved in this arthritic process, this cannot be regarded as a generalised arthrosis as only joints subjected to the mechanical overload are adversely affected.⁹⁰ These studies demonstrated that shear stresses from repeated impact loads can simulate the anatomical topology of osteoarthritic lesions such as fibrillation, horizontal fractures at the cartilage bone interface and thickening of calcified cartilage with tidemark reduplication. Fibrillations are in fact microfractures of articular cartilage. These lesions have a topological pattern identical to material failure in synthetic polymeric biomaterials.⁹² Animals with high repeated impact loads have more severe cartilage fibrillation than animals exposed to lesser loads. Further, rapid loading prevents the stress relaxation which occurs when water in cartilage flows away from high pressure areas. This results in transmission of greater forces to bone, stiffening the subchondral bone with eventual osseous microfractures.⁸⁷ While the direct effects of shear stress in cartilage and bone appear well established, the role of mechanical determinants on chondrocyte metabolism including the capacity of chondrocytes to produce and secrete matrix modulating enzymes remains to be determined. Within six weeks of repeated impact loading, Walker *et al* demonstrated synovial lining cell hyperplasia and sub-synovial fibrosis without preceding synovial neutrophil exudation.⁹¹ These features closely resemble human osteoarthritis. The early onset of these changes suggest that factors such as degradative enzymes elaborated by synovial cells may contribute to cartilage degradation.

In summary, experimentally induced biomechanical arthrosis models are useful for

simulating joint injury and repair. In selected models, a progressive degenerative arthritis can be modelled. Further, these models are useful to study both the adverse and beneficial effects of joint motion and joint loading on articular tissues.

Experimental structural arthroses

In contrast to biomechanical arthroses in which altered loads affect previously normal tissues, experimental structural arthroses are models in which the tissue composition of one or more structural components of joints is degraded. This structural alteration can adversely affect tissue mechanics resulting in increased susceptibility to injury and varying incapacity to complete the repair process. Structural arthroses can be monoarticular, confined to one tissue within a joint, for example, cartilage, or even restricted to one portion of a joint surface. Alternatively, local structural arthrosis models can be devised to affect tissues of an entire joint. In these models, the nature of the injury is controlled by the selection of the agent, the dose, and frequency of application. Polyarticular structural arthroses models either experimentally induced or identified as spontaneous disease in certain animal groups have been extensively investigated. As discussed below, the appropriate choice of model depends on the experimental question addressed.

Monoarticular structural arthroses

The vast range of noxious agents applied locally to joints bears testimony as much to the compositional strength and resilience of joint tissues, as it does to the breadth of investigators' imaginations or to the multitude of fallen hypotheses.^{10 14-21} Traditionally, local structural arthroses have been classified on the basis of aetiologic agent, for example, physical, chemical, enzymatic, immunological etc (table 6). More useful is the assessment of these models based on the selectivity of their action on target tissues or tissue components. Some agents have activity directed broadly against extracellular matrix or articular cells. Newer agents can target more specifically matrix components such as collagen or proteoglycan or specific biochemical pathways within chondrocytes or synoviocytes.

Analogous to the inter-relationships of biomechanical forces and structural changes, injury to extracellular matrix may induce inflammation, repair, and other cell mediated responses. Conversely, agents directed towards articular cells affect the capacity to maintain, remodel or regenerate extracellular matrix. In selected models, such as surgical defects,⁹³⁻⁹⁵ abrasion,^{96 97} contusion⁹⁸ or freezing⁹⁹ of articular cartilage, the lesions can be induced in an anatomically focal and controlled manner. At their best, these models are particularly useful to investigate how chondrocytes replicate in vivo and regenerate their matrix.

Models directed towards extracellular matrix and its components

Depending on the particular model, matrix injury may involve tissue materials globally or may target selectively one or more matrix components. The simplest of these models is surgical trauma induced by incision, shaving, abrasion,^{96 97} or contusion.^{98 100} While arguably these are micromechanical models, when abrasion is induced under some conditions, the heat energy generated degrades the subjacent matrix and causes regional chondrocyte necrosis.⁹⁶ Surgical extirpation of tissues to create a defect is a useful model to study the regenerative capacity of joint components. For example, surgical lesions of cartilage that do not penetrate subchondral bone usually fail to generate reparative tissue.^{101 102} Defects that penetrate the subchondral bone induce chondrocyte regeneration from reparative fibrocartilaginous callus growing in from the marrow. Altman *et al* have shown that cartilage repair occurs following extensive cartilage abrasion to the subchondral bone and that the tissue repair more closely resembles hyaline cartilage in animals previously subjected to anterior cruciate ligament transection than in animals that are subjected to abrasion alone.⁹⁷ As anterior cruciate ligament transection initially produces synovitis, this suggests that the synovial reaction can modulate cartilage repair.

More specific markers are now available to track phenotypic expression of cartilage cells following injury. For example, the chondrogenic potential of reparative cells can be followed throughout the repair process as these cells stain with the S-100 antigen.¹⁰³ Initially the matrix consists of a type I collagen rich fibrocartilage which under favourable conditions can remodel to hyaline cartilage composed of type II collagen.^{94 104} With larger defects, progressive disruption of the joint surface occurs.^{93 95} Depending on the conditions, intra-articular administration of agents such as heat, fixatives, protein denaturants, acids, alkalis, distilled water or ionic solutions can degrade the matrix, adversely affecting or killing only superficial articular cells.^{17 105}

Intra-articular administration of proteolytic enzymes such as papain,¹⁰⁶⁻¹¹⁷ trypsin,^{118 119} hyaluronidase¹²⁰ and collagenase^{111 115 121} are examples of model arthroses directed towards selective degradation of cartilage matrix components. At low doses, papain degrades proteoglycan transiently and spares the collagen framework. Within 48 hours there is acute synovial inflammation, cartilage proteoglycan depletion and chondrocyte necrosis. Subsequently cartilage oedema, proteoglycan regeneration, synovial cell and chondrocyte replication are features.^{112 116}

In this model, the capacity for complete repair can be shown to depend on cartilage collagen meshwork integrity.¹¹³ The mechanism and specificity of these models particularly papain and trypsin arthropathy must be questioned as early in the model, an inflammatory arthritis, which is dose dependent may

be a feature. This inflammation can be reduced by agents such as glycosaminoglycan-peptide complex.¹²²

In joints with surgically induced defects, chondrocyte regeneration can be enhanced by intra-articular administration of trypsin and blood.¹¹⁸ Intra-articular hyaluronidase injection produces degenerative changes in superficial cartilage, non-inflammatory synovial effusion, and striking hyperplasia of the synovial lining cells.¹²⁰ With more potent enzymes such as collagenase, there are associated degenerative changes in structures such as ligaments. This suggests that both direct effects on cartilage matrix degradation as well as instability caused by ligament matrix injury may contribute towards chronic articular degeneration in affected animals.^{111 115}

Models directed towards articular cells

Models directed towards inhibition of articular cells, predominantly chondrocytes, can be induced by physical agents such as freezing, electrolysis, or ionising radiation similar to that following intra-articular injection of ⁹⁰Yttrium (⁹⁰Y).¹²³ Chemical agents such as intra-articular injection of the cytotoxic drugs Thiopeta, nitrogen mustard,^{17 124} colchicine,¹²⁵ osmic acid,¹²⁶ or iodoacetate^{17 115 127} are capable of damaging articular cells selectively. For example, osmic acid, a fixative that has been administered intra-articularly for the therapy of rheumatoid arthritis, clinically and experimentally induces synovial fibrosis and functional impairment of residual synovial cells which contain osmic acid intracytoplasmic inclusions.¹²⁶ Critical to the tissue effect of a chemical agent is its ability to penetrate cartilage matrix. Hence osmic acid and colchicine are most active in synovium whereas an agent such as iodoacetate which diffuses into cartilage affects chondrocytes. The cell cycle of the target cells at the time of injury is also important. Under normal conditions, chondrocytes are in a non-proliferative phase of the cell cycle and may be resistant to agents which affect proliferating cells selectively. Other agents such as vitamin A,¹²⁸ and Filipin,^{129 130} by labilising cell membranes including those of lysosomes, stimulate chondrocytes to produce and secrete matrix proteolytic enzymes.¹⁸

Postinflammatory degenerative arthritis can be induced by intra-articular injection of agents which range from well defined compounds such as croton oil,^{131 132} autologous lipid,¹³³ carrageenin,¹³⁴⁻¹³⁶ zymosan¹³⁷⁻¹³⁹ and dextran sulphate¹⁴⁰ to complex substances such as allogenic cartilage particles¹⁴¹ or organisms, principally bacteria.¹⁴² Moreover, as noted above, agents such as papain which are primarily directed towards matrix components may incite joint inflammation as an early event in their activity.¹¹⁶ Usually the inflammatory arthritis induced by these agents occurs for a very limited time. Following inflammation, a chronic degenerative arthritis may ensue. Mediators of articular tissue degeneration in this form of arthritis are difficult to identify. Also, lesions induced by these methods result

in complex changes affecting both matrix and endogenous articular cells such as chondrocytes, synovial lining cells and subchondral bone cells.

These considerations have led to more controlled models in which specific biological mediators such as interleukin-1, tumour necrosis factor, substance P or transforming growth factor- β -2 (TGF- β 2) are injected intra-articularly.¹⁴³⁻¹⁴⁶ Intra-articular interleukin-1 injection in C57/BL/10 mice produces cartilage proteoglycan degradation and suppression of cartilage proteoglycan synthesis without antecedent inflammation.¹⁴⁴ These effects are prolonged in older animals. In these models, interleukin-1 (IL-1) has a more direct effect on proteoglycan synthesis inhibition than stimulation of proteoglycan degradation.¹⁴⁷ As matrix degradation following IL-1 injection is mediated by metalloproteinases, this model has been used to determine the protective effect of serine proteinase inhibitors such as protease nexin-1 (PN-1) on cartilage proteoglycan content.¹⁴⁸ Elford *et al*, injecting TGF- β 2 into rabbit knee joints induced synovial fluid and cartilage oedema, loss of cartilage matrix proteoglycan and synovial cell hyperplasia.¹⁴⁵ As these effects were produced without an increase in interleukin-1 α synthesis, this suggests that TGF- β 2 can act directly as a mediator of joint damage. Models of this type have the promise of inducing specific cellular activities, thereby providing models to study articular cell regulation by endogenous or exogenous agents.

The role of calcium apatite or calcium pyrophosphate dihydrate crystal deposition in osteoarthritic cartilage remains controversial. The few available experimental models are difficult to relate to human disease. Reginato and Schumacher reviewed models in which calcium apatite was deposited in joint tissues.¹⁴⁹ Systemic vitamin D and repeated intra-articular corticosteroid administration can both produce calcium apatite deposits in rabbit articular cartilage.¹⁴⁹⁻¹⁵³ These models are of considerable clinical importance as cartilage matrix proteoglycan biosynthesis is suppressed by corticosteroids but is restored following cessation of these agents.¹⁵²

Corticosteroid arthrosis appears to model the calcium apatite deposition which occurs spontaneously in the cartilage of old rabbits.¹⁵⁴ At present, no experimental method is available to induce calcium pyrophosphate dihydrate crystal deposition in articular cartilage.

An old but instructive example of local structural arthrosis is the model induced by the intra-articular injections of saline.¹⁰⁵ This model has recently been used by Vasilev *et al*¹⁵⁵ to study chronic synovitis beyond one month following injection. Two morphological features of chronic osteoarthritis, synovial lining cell hyperplasia and intrasynovial fibrosis develop within 60 days following intra-articular saline injections.¹⁵⁵ Although the specificity of these changes for osteoarthritis has been questioned,¹⁷ Soren has shown that without lymphocytic inflammation, these synovial features are characteristic of degenerative arthritis.¹⁵⁶

As models for the effects of synovitis and its sequelae, intra-articular injection of urate, calcium pyrophosphate dihydrate or cholesterol crystals have been used.¹⁵⁷ The effects of prolonged and more extensive synovitis can be studied by intra-articular injection of biologically non-degradable crystals such as magnesium tetrasilicate (talcum powder).^{158–160} The prolonged inflammatory effects of this agent involves mediators which activate cartilage and bone remodelling. Thus intra-articular crystal arthritis models should be regarded as a spectrum that include pure synovitis models, for example, urate, CPPD or cholesterol, and inflammation—cartilage degeneration models, such as, talcum powder injection.

Polyarticular structural arthroses

Spontaneous osteoarthritis in humans is commonly manifested as polyarticular disease.¹⁶¹ This suggests that metabolic factors drive the pathogenesis of this disorder. Despite its prevalence, identification of human generalised osteoarthritis particularly in its early stages remains difficult. Therefore model polyarticular structural arthroses may be particularly valuable to elucidate the key features of early osteoarthritis and to understand the genetic, nutritional and other factors that result in degenerative articular disease. There are two classes of models for polyarticular structural arthroses (table 7). Firstly, there are experimentally induced models in which a specific agent induces lesions with similarities to human osteoarthritis. Secondly, models can be developed from the study of spontaneous degenerative arthritis in animals. In these models, as in human osteoarthritis, the aetiological agent(s) and pathogenic mechanisms remain unknown.

Experimentally induced polyarticular structural arthroses

After the introduction in 1949 of cortisone for the treatment of rheumatoid arthritis, extensive research on the production and attenuation of arthritis was undertaken using a variety of

endocrine ablations and supplements.^{17 20 21} As useful as these studies were then, because of the lack of purity of endocrine extracts, frequency of inflammation, intercurrent infections and short time course of experiments, their relevance to clinical joint disease should be questioned.

The principle that nutritional and endocrine manipulation can promote the development of degenerative arthritis was demonstrated by the studies of Ruth Silberberg and colleagues.^{162–172} C₅₇Bl mice fed a high fat diet supplement, more specifically 4% cholesterol, developed knee and spine arthritis.^{168 169} Similarly the dietary substitution of Omega-3 fatty acids (Menhaden fish oil) for Omega-6 essential fatty acids (Safflower oil) produced cartilage fibrillation and ultrastructural retrogressive changes in rat chondrocytes.¹⁷³ An acute degenerative arthritis, interesting for its specificity to a particular region of cartilage, can be induced in immature animals by oral administration of quinolone analogues.^{174 175} These drugs cause necrosis in the mid zone of articular cartilage where chondrocytes are replicating. This results in oedema which simulates the chondromalacia observed in the patella of adolescent human adults. Although the mechanism of this arthropathy is imperfectly understood, quinolones preferentially concentrate in the mid zone of immature articular cartilage. These agents bind specifically to circular DNA. It has been suggested that chondrocyte necrosis in this model is induced by the toxic effects of quinolone on chondrocyte mitochondrial DNA.^{174 175}

Polyarthritis induced by autoimmunity relates primarily to rheumatoid arthritis pathogenesis. Nonetheless, there is considerable interest in how immune responses to cartilage degradation products such as Type II collagen and proteoglycan promote the progression of degenerative arthritis.^{176–184} The observations in these experimental disorders indicate that primary immunologically induced arthritis produces tissue effects substantially different from other models of osteoarthritis.

Spontaneous polyarticular structural arthroses

Spontaneous osteoarthritis models include types of spontaneous degenerative osteoarthritis that occur in species other than humans^{130 162 185–196} as well as studies of paleontological and osteological remains from humans and other species.^{197–200}

The isolated occurrence of degenerative arthritis in an animal or a group of animals does not in itself constitute an experimental arthritis model.^{89 201 202} While degenerative arthritis appears widespread amongst mature livestock and domestic animals, these groups are not usually available for research.^{89 203} Similarly, degenerative arthritis may occur commonly in feral or wild animal species. However, when these animals are incapacitated even slightly by arthritis, they are more likely to be available to predators than investigators. Thus the study of spontaneous degenerative arthritis

Table 7 Polyarticular structural arthroses

1	Experimentally induced arthroses
	Cholesterol feeding
	Omega—fatty acid feeding
	Quinolone antibiotics and derivatives
	Hydralazine
	Autoimmunity
	Cartilage proteoglycan
	Type II collagen
2	Spontaneous polyarticular arthroses
	Mouse (<i>mus musculus</i>)
	C ₅₇ Bl
	STR/IN
	NZY/BL
	ICR
	SAMP-3
	Rat (<i>Rattus rattus</i>)
	CD/BR Sprague Dawley
	Guinea pig (<i>Cavia porcellus</i>)
	Dog (<i>Canis familiaris</i>)
	Labrador retriever
	Beagle
	German shepherd
	Primates
	Rhesus monkey (<i>Maccaca mulatta</i>)
	Human (<i>Homo sapiens</i>)

has been confined to laboratory bred colonies of mice, rats, guinea pigs, dogs and more recently, rhesus monkeys.^{130 162 185-187 189-196}

Sokoloff, noted that degenerative osteoarthritis is rare in rats.²⁰⁴ It can be speculated that this phenomenon relates to the observation that most rat species retain functional epiphyseal cartilage throughout life. Consequently rat articular cartilage may have a less mature, more resilient composition than cartilage of other species. Recently Sokoloff's observations have been challenged by Mohr and Lehmann who studied the ankle joints of CD/BK Sprague Dawley rats, aged approximately 26 months. Histological features of osteoarthritis such as chondrocyte necrosis, cartilage fibrillation and subchondral bone plate remodelling were commonly found in these joints.¹⁹⁶ These investigations indicate that aged rats can be susceptible to osteoarthritis. However, the ankle joint is an unusual site as it is relatively spared in human disease.

Degenerative arthritis in laboratory bred mice has been extensively studied in the C₅₇Bl^{162-167 170-172} and STR/IN^{185-187 205-207} strains, the NZY strain¹⁸⁸ and in temporomandibular joints of ICR²⁰⁸ and SAM-P/3 strains.²⁰⁹ In some models such as the substrain of C₅₇BL/6 mice ultrastructural morphological abnormalities are evident in the superficial articular cartilage as early as two months of age.²¹⁰ Studies of genetically well defined murine models have been particularly suitable to demonstrate sex differences (male predominance), nutritional, and hormonal effects as well as the polygenic inheritance of degenerative arthritis. Limitations include the short life span of animals (circa two years),²¹¹ and the male compared to female predominance found in human polyarticular osteoarthritis. Further limitations include lack of correspondence of some morphological changes to human disease,^{171 186} and the small amounts of tissue available for study in each animal. Walton has ascribed the degenerative arthritis in STR/IN mice to biomechanical factors, namely joint instability related to a propensity for patellar dislocation. Surgical stabilisation of the patella in these animals eliminated the development of osteoarthritis in the medial femoral/tibial compartment.^{185 192 205}

Recently the temporomandibular joints of two further murine strains, ICR and SAM-P/3 (Senescence accelerated mouse—prone) mice have been studied.^{208 209} Quite apart from difficulties relating temporomandibular changes to other synovial joints, there is a lack of distinction between ageing and degenerative arthritic features in these animal studies.

Erosive and proliferative changes in cartilage with osteophyte formation has been observed in guinea pigs.^{189 212 213} The cartilage lesions are usually mild. Accelerated spontaneous degenerative joint disease which is often associated with hip dysplasia has been observed in breeds of large dogs.^{190 194 195 214 215} Lust *et al* have shown that compared with human osteoarthritis, the cartilage changes in a colony of Labrador retriever dogs appears relatively mild. Nonetheless, cartilage from osteoarthritic

animals differs biologically from controls particularly in fibronectin content.²¹⁵ Without hip dysplasia, degenerative arthritis occurs in old Labrador retrievers, as well as other canine species such as German shepherds and Beagles with a prevalence at necropsy of 35%.^{130 195 216} Because of the presence of spontaneous degenerative joint disease in such species as guinea pigs and dogs, caution is required to interpret long term observations following experimentally induced biomechanical arthrosis such as anterior cruciate ligament transection in these animals.^{33 35 217} Two forms of degenerative arthritis, calcium pyrophosphate dihydrate crystal deposition disease^{12 218} and osteoarthritis^{13 219} have been demonstrated in the rhesus macaque (*Maccaca mulatta*). While frequent in the most elderly animals, the difficulty of identifying early CPPD crystal deposition disease clinically has to date precluded the development of this species as a model for crystal deposition disease. In contrast, osteoarthritis appears in these animals following epiphyseal closure and progresses throughout life. The model is amenable to study as the disease has a high prevalence, age matched controls are available, the animals are free ranging, and the matrilineages can be clearly identified.^{13 219} Further, the joints are sufficiently large to be suitable for radiological studies including MRI,^{220 221} biochemistry, and histology^{191 193} (figs 1-4).

Osteoarthritis in the rhesus macaque develops from the age of five to 15 years, an accelerated process compared to humans but sufficient to develop structural, chemical, and biochemical^{13 191 193 219 220} changes in joints that closely resemble the features of polyarticular osteoarthritis in humans. Because of the extended time over which the osteoarthritis develops, this model is particularly suitable for the study of changes in cartilage collagen. As the organisation and distribution of cartilage collagen may be critically important to the

Figure 1 Anterior-posterior radiograph of rhesus macaque knee joint with osteoarthritis. Note joint space reduction, subchondral bone sclerosis and marginal osteophytes (V).

Figure 2 Parasagittal proton density MRI of rhesus macaque osteoarthritic knee joint. Note the thinning and disruption of articular cartilage particularly on the anterior femoral condyle (V).
WR = external water reference.

progression of osteoarthritis, this model may be particularly useful for assessing these changes.²²⁰ Because of similarities of rhesus macaque physiology to humans, this model may prove particularly valuable for demonstrating the role of systemic factors including the role of obesity in the development of degenerative arthritis. The tropical location and the vegetarian diet (Monkey Chow)²²² of these animals indicates that the degenerative arthritis can develop spontaneously independent of temperate weather or human eating habits. Two special resources for this model are concurrent social anthropological

Figure 3 Femoral condyle of an osteoarthritic rhesus macaque. Note the loss of cartilage, bone eburnation and articular surface deformation on the medial condyle.

Figure 4 Photomicrograph of articular cartilage from an osteoarthritic knee joint of a rhesus macaque. Note the fibrillation, erosion and loss of staining of the superficial cartilage matrix.
Toluidine blue stain magnification $\times 100$.

studies in the colony^{223 224} and the preservation of osteological remains from the entire population.^{198 199}

While social correlates in this model remain to be determined, on the basis of osteological studies in this and other rhesus monkey populations, deRousseau identified the presence and demonstrated the prevalence of osteoarthritic lesions.^{198 199}

The value of osteological studies to demonstrate the prevalence, nature and severity of degenerative arthritic lesions has been shown by Rothchild.¹⁹⁷ These studies indicate that osteoarthritis is a disease of antiquity in humans and that degenerative joint disease occurs widely in both Old World and New World primates as well as other species.¹⁹⁷ Osteological studies of prehistoric human populations such as the Inuit have provided insight into physical activity induced monoarticular and auciarticular forms of degenerative arthritis. Presumably this study reflects osteoarthritis resulting from displaced joint loading.²²⁵ Currently the utility of osteological models is hampered by the lack of precise correlation of osseous observation with soft tissue and cartilage features as well as the differing terminology amongst osteology, radiology and pathology disciplines.

Cross-over or mixed models

A promising application strategy for osteoarthritis models involves the controlled use of one model within another. This approach is not new. For example, administration of

high fat diets,^{163 168 169} or testosterone^{164 165 167} to C₅₇Bl mice that constitutionally develop degenerative joint disease, accelerates the severity of the arthritis. Recently, Bendele *et al* studied the effects of iodoacetate, a chondrocytotoxic compound administered intra-articularly before partial meniscectomy or collateral ligament sectioning in the guinea pig model of osteoarthritis.¹²⁷ No differences were observed in the cartilage of iodoacetate treated groups compared with controls. This suggests that chondrocytes do not contribute actively to the initial reaction of instability induced injury. Altman *et al* studied the effects of full thickness chondral abrasion in the Pond-Nuki model of anterior cruciate ligament transection. They demonstrated that cartilage repair in the presence of instability was facilitated by exposure to subchondral bone that resulted from abrasion.⁹⁷

Carney *et al* using the Pond-Nuki model of anterior cruciate ligament transection studied proteoglycan biosynthetic properties of cartilage explants in culture.²²⁶ Cartilage proteoglycan synthesis following ligament transection showed quantitative differences both in proteoglycans synthesised and in breakdown products.²²⁷ This suggests that chondrocytes in these animals have undergone phenotypic changes which can persist under *ex vivo* conditions. Mixed models have shown that after arthritis is induced, cartilage cells can maintain new phenotypic characteristics *ex vivo*. For example, Schalkwijk studied cartilage from C₅₇Bl/10 mice with arthritis induced by intra-articular zymosan injection. Chondrocytes from the affected animals were more resistant *ex vivo* to the anabolic effects of insulin-like growth factor-1 (IGF-1).¹³⁸

Animal models for osteoarthritis: prospects

In his monumental review of experimental arthritis published in this journal in 1960, Dugald Gardner pointed out that although numerous experimental models for arthritis had been employed for over a century, none was strictly mimetic for human disease.¹⁷ Recently, Leon Sokoloff has suggested that the value of animal models must relate to the correspondence of structural and functional features within the model to those of human disease.²²⁸ This task is especially difficult for osteoarthritis. As Sokoloff points out, osteoarthritis remains broadly defined as a heterogeneous group of disorders, causing progressive degeneration of joint tissues. Without visible anatomical lesions, such definitions do not distinguish differences in tissue composition associated with osteoarthritis from those associated with ageing, or from reactions to biomechanical, toxic, or inflammatory injury.

Cartilage hypertrophy following anterior cruciate ligament transection provides a currently controversial example of tissue compositional change in an animal model. The controversy resides in whether cartilage hypertrophy relates to oedema following acute

injury, to repair, or to progression of osteoarthritis.^{32 33 35 217 229 230} Present evidence indicates that chondrocytes replicate in this model³² similar to other injury models such as papain¹⁰⁹ or trypsin¹¹⁹ and that cartilage hypertrophy occurs because of an increase in water content accompanied by an increase in proteoglycan swelling, synthesis, and extractability.²³⁰ Cartilage hypertrophy related to oedema is an early feature of human osteoarthritis,²³¹ particularly in articular cartilage volumes subject to increased biomechanical stress. In established osteoarthritis, however, cartilage hypertrophy present in both weight bearing and non weight bearing sites may relate more closely to its collagenous architecture than to its proteoglycan content. These compositional differences can be assessed in appropriate models of polyarticular structural arthroses.

To assess joint tissue composition before visible lesions are present, two new techniques are available: analytical MRI^{112 220 221 232 233} and histological image analysis.²³⁴ MRI can determine not only the volumes of joint soft tissues and cartilage but can assess water quality within joint cartilage.^{112 220 221 232 233} Quantitation of histological data by image analysis can establish more precise topological relations between cells and extracellular matrix components of joint tissues. The application of confocal microscope with capabilities for three dimensional reconstruction of joint tissue architecture including the distribution of minor structural components, enzymes, and trace molecules holds particular promise.²³⁵ Serum and synovial fluid markers for clinical assessment of osteoarthritis are presently disappointing. However, in association with the production of specific lesions, animal models are becoming useful in the search for serum and synovial fluid markers of cartilage osteoarthritic activity.²³⁶⁻²⁴²

It is likely that greater precision in construction and analysis of osteoarthritic animal models will circumscribe and identify specific patterns of tissue composition in diseased joints. This will facilitate distinction of patterns associated with genetic, constitutional and biomechanical determinants of osteoarthritis from each other and from those of normal ageing. Now that new and more precise methods of assessing tissue composition are available, correlation of tissue patterns with osteoarthritis determinants is dependent on more precise characterisation of each determinant. Ambitious as this may seem, several promising approaches exist or appear to be on the near horizon. Genetic analysis of spontaneous osteoarthritis models is now available by DNA fingerprinting.²⁴³ It is now feasible to induce selected molecular defects in structural proteins such as collagen by genomic manipulation of transgenic mice.²⁴⁴ Structural arthroses can be induced selectively to affect certain extracellular matrix components or via cytokines and other mediators to modulate a restricted range of articular cell activity.^{145 146} Spontaneous osteoarthritis models can be used to assess each tissue change as osteoarthritis develops. These changes can be compared with

both age matched controls and to changes in human disease. As knowledge develops, the role of systemic factors that affect osteoarthritis activity or progression can be tested in these models. As biomechanical models become more refined, these studies will relate the applied forces to mechanisms of absorbed energy dissipation including changes in matrix water movement, conformation of matrix macromolecules and articular cell activity. Clearly, biomechanical and structural arthroses are complementary models for osteoarthritis. Emerging from future research with animal models, we can expect a better understanding not only of osteoarthritis oetiopathogenesis but also of joint biology in general.

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