Joint forces have a high potential to promote degenerative changes in articular cartilage. Researchers have not yet developed a material that simulates natural articular cartilage, and replacement procedures have finite lives. In all patients, regardless of diagnostic category, the impact of rehabilitative procedures on the integrity and health of articular cartilage should be a consideration. In this paper, I will review why articular cartilage breaks down, how cartilage lesions are classified in vitro and in vivo, as well as cartilage's capacity for repair and repair enhancement. The primary focus will be on processes and procedures that impact physical therapy. Review sources included common computer-based search instruments and literature in all languages. This research showed that most studies have been conducted on animals, which differ in important respects from humans. Such studies, however, provide guidelines for physical therapists. Unloading and overloading are detrimental to articular cartilage. Research indicates value in controlled, progressive regimes that alternate load and non-load conditions.

**Key Words:** articular cartilage, pathomechanics, rehabilitation

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**Pathomechanics or What Causes Cartilage to Break Down?**

The extracellular matrix, synthesized by chondrocytes, gives articular cartilage its specialized loading and mechanical properties, such as the ability to withstand both static and dynamic loading stresses. The absence of vascularity, however, is a critical factor in articular cartilage's inability to respond to injury with the typical stages of inflammation and seriously impairs its repair capacity. The chondrocyte is at particular risk because of this location in an avascular matrix, which creates a long transit route of its nutrition from sub-synovial capillaries through synovial lining tissues, synovial fluid, and cartilage matrix. Matrix destruction results from an imbalance between anabolism (synthesis) or catabolism (breakdown).

Mechanisms of articular cartilage breakdown involve multiple factors and imbalance between extracellular matrix degradation and synthesis. Radin (82) considers repetitive impulsive loading to be a major factor. Other factors are stress deprivation (immobilization, bed rest, weightlessness), excessive loading (extrinsic as in carrying heavy loads and intrinsic as in obesity, which is a statistically significant factor in osteoarthritis of the knee joint), malalignment as a result of developmental etiologies (for example, patella alta (49), tibial vara, joint surface incongruity) and joint instability (cruciate ligament trauma, meniscectomy, generalized ligamentous laxity).

The type of stress to which cartilage is regularly subjected appears to condition the structural and functional properties of articular cartilage (92). There is also evidence, from canine studies, that the biomechanical response to stress, such as long distance running, is highly site-dependent.
Degenerative cartilage exhibits extensive damage to type II collagen fibers, eventual unwinding of the helix, and the appearance of collagen fibrils (81). This process appears to commence in the superficial layers and progresses to the deep layers. While cartilage proteoglycan loss can be reversed, loss of the structural integrity of cartilage and its collagen framework results in irreversible disintegration of the cartilage (22,44). Repair is with fibrocartilaginous tissue in which type I collagen, rather than the normal type II, predominates. This has negative consequences as it may facilitate calcification of repair tissue; only type II collagen, now decreased in quantity, has the capacity to block the deposit of hydroxyapatite crystals required for calcification. As will be addressed in a later section of this paper, there is some evidence that given time type II collagen may replace the type I collagen formed initially with insult to healthy (that is, not degenerative) cartilage. This process may take up to a year and may be incomplete (6,28,71).

Collagen turnover increases in conditions which increase in prevalence with aging, such as hypoparathyroidism and metastatic diseases of bone (81). The degradation of collagen under these conditions or diseases provides the body with a source of amino acids. It is hypothesized that, in these conditions, articular cartilage is more vulnerable and should not be subjected to heavy loading stresses. It is suspected that mechanical forces, or enzymes, may degrade the “glue” that binds the collagen fibers into a network and be a contributing factor in pathogenesis of cartilage degeneration leading to osteoarthritis (15).

**Influence of temperature** The enzymatic processes in cartilage breakdown involves both chondrocytes and synoviocytes; both can produce degradative enzymes and protease inhibitors. Matrix pH and physical factors, such as temperature, influence the enzymatic activity. Collagenase is more active at high joint temperatures (36° vs. 33°C) (68). If cells are even mildly heated, they synthesize heat shock proteins, which are found in synovia from arthritic joints. Heat shock proteins are molecules produced in response to various stimuli with an ability to bind to and influence the intracellular function and distribution of other proteins. They appear to provoke a cellular stress response. It is believed that the temperature of an inflamed joint has the adverse effect of inducing synthesis of these proteins (36,119). In rheumatoid arthritis, serum antibodies to these proteins are present. Such data support the use of cold over heat in acutely inflamed joints.

**Matrix components** The mechanical resilience of cartilage matrix is dependent on the chondrocyte’s ability to maintain its constituents in normal proportions. The extracellular matrix is composed of collagens, proteoglycans, noncollagen proteoglycans, and water (65-80%). Major components of proteoglycans are the polymers, chondroitin sulphate and keratan sulphate, members of the group of polysaccharides called glycosaminoglycans or mucopolysaccharides. The ratio of chondroitin sulphate and keratan sulphate varies with age, site, and between individuals (22). The ratio of chondroitin sulphate and keratan sulphate is a factor in the fixed charge density which controls the distribution of charged solutes and, hence, osmotic pressure. Keratan sulphate concentration has been shown to increase with aging and, in osteoarthritic cartilage, decrease with immobilization, and may contribute to cartilage pathology (14,22,47,64,102). Increased proportion of keratan sulphate vs. chondroitin sulphate appears to be a negative change impacting matrix stiffness, its ability to bear loads, and dissipate forces through cartilage.

**Inflammation** The typical inflammatory response to injury or pathol-
ogy is more visible in the most vascular joint tissue, the synovial lining tissue. Synovitis may result from a variety of stimuli and creates an environment that is hostile to articular cartilage. Such stimuli can include substances normally foreign to the joint space, such as cartilage wear particles, matrix molecules, immune complexes, hemosiderin (an iron blood corpuscle pigment), implant wear particles (ie., from artificial ligaments), hydroxyapatite (released from bone matrix), and surgical chemical agents (ethylene oxide, glutaraldehyde) (85). The absorptive synovial intimal cells take up such substances which have been shown to persist indefinitely in the intimal layer. This process, however, may cause the intimal cells to secrete substances that are harmful to articular cartilage and provokes a chronic inflammatory reaction.

The enzymatically degraded cartilage releases proteoglycans, which may also activate the synovial cells (so termed “suicide” reaction, where cartilage hastens its own destruction). A vicious cycle develops with synovial intimal cells releasing more collagenase and proteinases, cytokines, and interleukin-1, which further weakens the cartilage and enhances mechanical damage (16,80,94). Type B synovial cells may be primarily involved in this reaction. Collagenase, gelatinase, and stromelysin can digest the collagenous lattice within the articular matrix (26). Type A synovial cells are believed to release cytokines (chemical messengers), such as interleukin-1 and prostaglandin E2, which may play a major role in the perpetuation of synovitis (39). Interleukin-1 is an inflammatory mediator that can cause chondrocytes to decrease matrix synthesis and resorb their surrounding matrix. Synovial cells are also activated by the proteoglycans released from enzymatically digested cartilage and may influence the immune response (39).

**Intra-articular pressure** Clinicians should recognize that effusion compromises joint stability because the intra-articular pressure that is normally negative becomes less negative or achieves a positive value. A patient with a knee effusion will adopt a posture of about 30–40° of flexion when cavity tissues are under the least tension (Figure 1), (94). Motion away from this position, particularly active motion, will increase intra-articular pressure and the potential for pain. As strain is increased on supporting structures, such as ligaments, the joint is less stable (Figure 2) (13, 40).

Changes in either the synovial lining tissues or the articular cartilage impact the normal lubricating mechanisms of the joint. The boundary lubricating ability of synovial fluid becomes more important when synovial fluid loses its viscosity due to injury or disease. Loss of cartilage compliance, that is its ability to deform under loading, increases with aging and reduces the ability to maintain fluid film by the squeeze film or elastohydrodynamic mechanisms (both have fluid extruded from unloaded areas of the cartilage; elastohydrodynamic includes cartilage compliance in the model). Theoretically, such conditions lessen the ability of cartilage to withstand static and/or high loading. Static or high loading are common states in the knee joint complex, as in such activities as ascending or descending ramps and stairs and rising from lying. Many sports activities are associated with very high loading conditions.

**Effect of Unloading and Immobility—Rest**

Articular cartilage is sensitive to abnormal loading. When unloaded
Lauren's and deprived of mechanical stimuli, there is rapid deterioration of biochemical and mechanical properties; cartilage becomes less stiff and is more vulnerable to injury. Mechanical forces, such as loading, may be more important than motion in maintaining cartilage properties; joint movement in the absence of loading was associated with cartilage atrophy (76), and such studies strongly support this contention.

Unloading Studies of denervated and immobilized joints support the suggestion that chondrocytes are sensitive to mechanical stimuli (99). In disuse atrophy, such as in paraplegia (27) or poliomyelitis (30) and denervation (3), chondrocytes showed increased synthetic activity with mechanical stress and lower activity with decreased compression on the load-bearing surfaces. A decrease in the thickness of articular cartilage (atrophy) and chondroitin sulphate observed in these conditions was also reported, with a decrease in glycosaminoglycan synthesis, in studies using animal models and hind paw amputations (46,105). Partial amputation of a limb decreases compression while allowing motion in the remaining joints. Under these conditions, adult rabbits may show changes within 1 week; however, in dogs, similar changes may take 11 weeks to be detectable (35,50). Cultured chondrocytes reportedly respond to mechanical stress in a comparable manner to articular cartilage in vivo (109). Collagen synthesis, but not the total amount of collagen, may be enhanced. Effects of unloading on collagen may occur in all collagenous tissues. Fiber-fiber distances and lubrication between fibers is decreased. This hinders fiber-on-fiber gliding and enhances cross-linking and adhesion formation (112). The collagen arrangement is more random. Fibers may be thicker, as fewer fibers are laid down with regard to the tissue’s mechanical requirements (115).

Variability in results of different studies relates in part to problems in the use of animal models, such as differences in species and age and variability in methods, for example, the position of immobilization, the degree of compression of the joint surfaces, and the extent that motion is limited. Reduced loading studies support the view that maintenance of healthy joint surfaces requires a regular program of loading. Encouraging individuals of all ages to walk regularly should be beneficial.

Inflamed joints are subjected to unloading and temporary immobilization for short time periods. As rest is a basic principle of inflammation management, whatever the cause, the negative effects of immobilization of joint tissues produce a dilemma: how to determine the balance between the period of rest to decrease inflammation, yet not incur further functional loss? Effusion reduction (thermal applications) with anti-inflammatory drug therapy are important components of treatment. If cartilage that has been atypically unloaded is then loaded, there may be "gross functional failure of matrix" (75). This appears to be related to a defect in the ability of proteoglycans to reform the hyaluronic acid-binding region of the aggregates. Impairment of the proteoglycan matrix may make articular cartilage more vulnerable to injuries if exposed to sudden, heavy loading. Studies on animals suggest that such changes may be reversed by a gently graduated program; however, restoration of healthy structure and characteristics is uncertain (101). Therapists should recognize that following immobilization or unloading (prolonged rest), articular cartilage is less stiff and less capable of tolerating high loads, loads that normally are within the physiological capacity of healthy cartilage. These results suggest that there is a need for programs of graduated weight bearing and activity after particularly extended periods of non-weight bearing and/or casting.

Immobilization Immobilization should prevent motion. Depending on the joint position, either an increase or decrease in loading to areas of the joint surfaces may occur. This limitation in motion results in degenerative changes that are similar to that seen in osteoarthritis and may result in cell necrosis (43,37,42,46,104). When clamps are used to produce immobilization (knee joint in small animals), clamping may also have caused compression of the articular cartilage (29,33,43,90,107,108). Cell death occurs with rigid, sustained pressure at focal points of the articular cartilage. Presumably, there is interference with cellular nutrition which is dependent on the cyclic compression and expansion of articular cartilage that occurs with normal intermittent loading (99). Simple diffusion of small solutes may be unaffected by cyclic loading (106). Permeability of cartilage decreases with compression of loaded areas (41) (Figure 3). Maroudas indirectly demonstrated that permeability of cartilage correlated inversely with hydration (66). Large deformation of cartilage will regulate the manner and rate of fluid transport; the more rapid the applied load, the more rapid the efflux at the edges of the loading surface, as well as movement of free fluid from superficial to deeper layers. It must be recognized that, in healthy cartilage compared with pathological cartilage, under any condition, fluid movement is minimal because most fluid is bound or constrained by the collagen lattice framework of the extracellular matrix.

Simple immobilization without compression also causes atrophy and
thinning of the articular cartilage but no change in cell density (41,98). Other changes include a decrease in glycosaminoglycans and chondroitin sulphate compared with the nonoperated or immobilized side (25), whereas intermittent compression of articular cartilage causes the reverse (75,109,111). With the atrophy of articular cartilage that has been observed in immobilization, there is also an enhancement in collagen synthesis (greater collagen fiber diameters) but not in the total amount of collagen (51,78,113). Tammi et al (100) used splints to immobilize dogs and showed a 53% increase in collagen production. In comparison, there was only an 11–13% increase in the dogs who ran on a treadmill for 15 weeks. Variability in results of different studies may relate to age of the animals, type of immobilization, and that some areas of the cartilage joint surface are subjected to increased loading while other areas are unloaded, dependent on the position of immobilization. The incongruity between the femoral and tibial con-dyles, as well as the varying contact between the patella facets and the femoral surface dependent on the joint position, makes this more likely in the knee joint.

When immobilization is an essential component of patient management, as for fracture management or following surgery, clinicians should devise exercises that will provide loading to immobilized joint surfaces. As yet, there are no studies to demonstrate whether this approach would result in "stronger" cartilage.

Increased Loading—Compression

Cartilage degeneration is associated with excessive mechanical loading (such as repetitive impulse loading) that produces fatigue fractures, microscopic cracks in and around osteons that involve individual trabeculae, and, over time, reduces the strength and stiffness of bone. If the damage is excessive, resorption will exceed deposition and failure will occur at the macroscopic level, as in crush fractures and contour changes in joint surfaces. These changes in bone place further stress on articular cartilage. Research has not yet established if such microcracks can trigger a cellular response to bring about repair of the damaged matrix.

There have been a number of experiments in which the joint surfaces have been abnormally loaded. Non-weight bearing on one limb creates an increased and altered load on the weight-bearing side. Studies in which the opposite limb joint(s) was used as a control(s) then have imperfect control tissue. Backpacks may be put on the animal, or weight gain may be simulated as in experiments performed by Simon et al with rats (95). Severe excessive loading experiments have employed the "drop tower" procedure to subject articular cartilage to high stress levels. These studies have shown that chondrocytes can survive up to a 30% compressive strain, but if the stress exceeds 250 g/mm² and produces a strain that is greater than 40%, tissue death results (84). This type of impact loading results in a loss of proteoglycans, fibrillation of the surfaces, and cell death (83). When loaded tissue extrudes interstitial fluid, it becomes less hydrated, resulting in an increase in the proteoglycan concentration which then, in a feedback mechanism on chondrocytes, inhibits its own synthesis (99). In vitro studies have revealed that static compressive pressures consistently inhibited proteoglycan synthesis in cartilage (77). Review of the effects of exercise suggests the response to cyclic compressive loading is more variable.

Excessive loading may occur in various sports, especially those that subject joints to impact and/or torsional loading, such as in ice skating with repetitive jumps and landings on a hard surface. Studies (7,56,59) suggest activities such as jumps should be interspersed with much longer periods of nonimpulsive loading to allow reconstruction of the cartilage following severe compression. There are implications for both rehabilitation and training routines. Loading activities, such as treadmill walking and step machine usage, should be followed by a period of exercise which unloads the previously loading joints: swimming or trunk or arm exercise in a different position, i.e., lying.

Effect of Exercise

While many therapists believe that joint motion improves circulation and, thus, nutrition to articular cartilage, van Kampen and van de Stadt (109) following review of in vitro and in vitro studies concluded that nutrition plays only a minor role in the processes involved in articular cartilage’s adaptation and response to under or overloading. The role of exercise in cartilage breakdown is unclear. Although some investigators have shown negative changes following exercise (10,11,24,57,110,113,114, 116), positive effects of exercise have been demonstrated (48,55,60,79,86–
The type of exercise influences the response. There were more degenerative surface changes in the femoral heads of rabbits with “sudden maximal” exercise compared with submaximal running (24). Several in vitro studies have shown that the chondrocytic response to loading, particularly cyclic stresses, may vary with the length of the treatment. Palmoski and Brandt (75) subjected cartilage plugs to static and cyclic stresses that were equivalent to about 1.5 times body weight. They demonstrated a positive response, a 38% increase in synthesis of glycosaminoglycans with a cycle of 4 sec on/11 sec off, but also a negative response, a decrease with a cycle of 60 sec on/60 sec off (75). This varied response has been shown both in cell cultures and in chondrocyte cultures (79). The response varied with the frequency of the pressure, duration of the application, and the state of the cells. Application for 1.5 hours produced a strong inhibitory reaction, whereas a 20-hour exposure produced a positive reaction, stimulation of sulphate incorporation (77). Response variability may relate to the observation that it may take 1.5–2 hours for complete aggrecan molecule synthesis, a finding which physical therapists should consider in planning therapy because aggrecans contribute to cartilage’s ability to withstand loading. It suggests the use of alternating periods of unloading and loading and, in the early stages of rehabilitation, unloaded periods should be longer than the loaded periods.

When cartilage explants were exposed to cyclic stress of two different frequencies (high: 2 sec on/2 sec off; low: 60 sec/60 sec off), there was a decrease in protein and proteoglycans synthesis with low frequency and static loading, whereas, in the high frequency cycle, there was a stimulatory effect on protein and proteoglycan synthesis (61). Unloading restored the synthesis to the preloaded levels. Results of these studies suggest that in the early stages of rehabilitation unloaded, quicker movements should be used. When static loading is introduced, time in unloaded conditions should follow and be of a longer time interval. Research is vitally needed to determine how different exercise regimes affect in vivo cartilage.

It should be noted that in vitro studies expose the tissues to only one type of stress, with forces that are mostly lower than the physiological levels experienced in vivo, such as at heel contact and toe-off in the gait cycle. Studies on knee joints of quadrupedal animals record forces in an individual joint that would be higher in bipedal humans. Quantitatively, contraction of muscles may result in greater forces across articular cartilage than does normal weight bearing (16). For instance, while 4–5 × body weight (BW) may be transmitted through the knee in walking, the force may be as much as 10 × BW in squatting (97). Similar reaction forces are estimated to occur in gymnastics (take-off vertical forces = 3.4–5.6 × BW) (18). High transarticular forces can be predicted for all jumping. Studies do show that joint surfaces can tolerate higher dynamic than static forces. It is also important to recall that loading is not uniform in the human knee joint and varies between condyles and compartments (19,23,92).

As microtrauma is cumulative, it is important to remember that equipment can play a major role in dampening joint forces. Is the footwear worn appropriate to the activity and in sound condition? A new mat in gymnastics was shown to reduce tibia accelerations from 50 to 10 g and hip accelerations from 20 to 8 g (18). Sheep that had walked for long distances 4 hours/day for 12–30 months on concrete floors demonstrated negative effects in knee articular cartilage, but these changes were not seen in those that walked on wood chips (83). If practice and performance jumping times are summed from sports, such as parachuting, burdelling, or ice skating, it is obvious that these activities result in high repetitive impulsive loading to joint surfaces.

Tammi et al (101) reviewed studies of various animal species involving “enhanced loading,” which have produced mixed results as to whether running exercise injures or does not injure articular cartilage. One factor in the variability of results may be the rate at which the program is commenced (101). A conditioning period seems important. The positive effects on articular cartilage of enhanced loading in the form of moderate running (eg., 4 km/day) are reversed by strenuous running (eg., 20 km/day). Whether the response to nonstrenuous exercising in human athletes is similar to that of animals, mainly dogs, is not yet known. The limits of the “physiological range” (Figure 4) and the response of mature articular cartilage in vivo needs to be determined. Study results suggest that ex-
exercise involving loading should be progressed gradually.

In summary, cartilage breakdown has multifactorial causes and the mechanism is not fully understood. Abnormal loading, be this excessive or reduced, whether from sustained static positioning as in immobilization or from activity/exercise or sport, changes cartilage properties and makes it more vulnerable to injury. Comparison of results from different studies requires a valid and reliable system of classifying cartilage damage which is used by different investigators.

**Classification of Defects**

Currently, we lack a reliable, feasible method of monitoring the state of joint cartilage in vivo. It is not feasible to biopsy articular cartilage. Even in osteoarthritis, “the criteria for diagnosis and classification on the basis of clinical and/or radiological presentation of even the overt stages of osteoarthritis are under dispute” (63). Lohmander noted that some sets of criteria in use neglect to even mention damage to the central issue, that of the joint cartilage itself (63). For example, in osteoarthritis of the knee, radiological criteria include the presence of osteophytes (spurs), narrowing of the joint space of one or more compartments, especially with weight bearing, subchondral sclerosis, and cysts (5). Such a list, however, does not include cartilage damage. Similar to goniometry, intraobserver error on reading of radiographs varies at different joints, and two readings by one observer has closer agreement than two readings by separate observers (5,53). Advances in radiology, such as magnetic resonance imaging (MRI), may enable in vivo detection of cartilage detail, especially its response to loading.

Classification of tissues has a key role to play in the interpretation of results among groups of samples, between patients and between animals and humans. There is a need to develop a diagnostic/disease progression method that will enable integration of clinical findings with biochemical, biomechanical, etiological, and histological evidence. The following discussion of grading systems to classify cartilage defects focuses on histological and postmortem material; complex rating/classification systems used clinically for knee disorders will be covered elsewhere in this special issue. Classification or grading systems that have been used on autopsy or histological materials are presented in Tables 1 and 2 (52,60,64,69,70,93,116). Most are descriptive at best; semi-quantitative and reliability rarely has been given. Most lack adequate definition between grades, while sometimes grades appear identical. Some of the differences between reported systems relate to differences between studies, in which only gross examination of the surface was conducted, to studies encompassing gross examination, histochemistry, and morphometrics. Gross examination may include Indian ink applied to the cartilage surface which allows identification of smooth to deeply fibrillated cartilaginous surfaces. Grading systems can be used with this method, which is regarded as an excellent preliminary technique, even with only slightly abnormal surface cartilage (73).

Mankin et al in 1971 (64) (Table 2) provided the most in-depth histological classification based on combining scores for several different parameters, which can then be grouped for an estimate of disease/damage severity (67). Mankin et al used four criteria with subcategories for three of the criteria. The composite score ranges from 0, completely normal, to 12–15 (almost completely disrupted). This system has been used most frequently. The limitation of the Mankin et al system is that it is not known if graduations, as measured by the composite score, are related in a linear fashion to the disease process (73). For example, a smooth surface or partial clefts may be strongly related to say, the Safranin staining score.

The absence of reliability testing is a weakness of many reports, and it is obvious from use of systems reported in the literature that most probably would have unacceptable reliability. Jurvelin et al (52), who reported reliability of their grading system (Table 2), noted that “qualitative methods are the basis for quantification, but are not sufficient in themselves.” They advocated classification of structural details present and the need for determination of the proportion of each type/category across the entire surface. Their sys-

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**TABLE 1. Grading systems for postmortem material at the macroscopic level.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Material</th>
<th>Grades</th>
<th>Reliability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennett et al (14)</td>
<td>Human postmortem</td>
<td>1+ uneven, granular surface, furrows NR</td>
<td></td>
</tr>
<tr>
<td>Kiss et al (54)</td>
<td>Human necropsies</td>
<td>0 intact system</td>
<td>12-15</td>
</tr>
<tr>
<td>Mitrovic et al (70)</td>
<td>Autopsy human</td>
<td>A+ bone exposed over whole surface</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

NR = Not reported.
Material
Grades
Reliability
Lanier (60) Mice 1. Minimal roughening, fibrillation, and splitting, extending to but not involving calcified cartilage
2. Degeneration extending into calcified cartilage, loss of surface not extending into subchondral bone
3. Lesions involving subchondral bone, thickening, and eburnation of cortex
None reported
Mankin et al (64) Human 1. Structure, six subcategories: Two observers, samples repeated for validity, variation estimated at <3%
2. Surface irregularities
3. Pannus and surface irregularities
4. Clefs to transitional zone
5. Clefs to radial zone
6. Clefs to calcified zone
7. Complete disorganization
Jurvelin et al (52) Rabbit patella Scanning microscopy
1. Evenness of surface six subcategories (even, slightly uneven, hillocky, folded, fibrous, unclassified) two investigators of 346,
2. Roughness of surface six subcategories (even, slightly rough, rough, knobby, leafy/striated, unclassified)
3. Splits of the surface six subcategories (intact, superficial splits, deep splits, unclassified) plus a computer-drawn map of joint surfaces
Total and mean area of each class
Minimum, maximum, and relative area (%) of each class compared with whole cartilage surface
N = 10
Mean difference between two investigators of 3%, variation 5%; one person did all evaluations
Walker (116) Rat knees 1. Surface only fraying, fibrillation, small defects in uncalcified cartilage layer (UCL) with abnormal staining reaction
2. Surface defects extended into UCL, cracks, holes in UCL, observed in 10–20% of sections
3. Prominent defects, multiple defects within a single section, defects extending from surface to tidemark, present in >20% of sections, marked abnormality of cartilage
Shortkroff et al (93) Dogs, chondral and osteochondral defects Grades for Masson-trichrome stained sections
0 = No positive staining
+ = Faint staining (< than normal)
++ = Moderate staining (same as normal)
+++ = Intense staining (more than normal)
Safranin-O stained sections:
0 = No positive staining
+ = <25% staining
++ = 25–50% staining
+++ = >50% staining
None reported

TABLE 2. Grading systems, light and scanning electron microscopic methods.

term was supplemented with a computer-drawn map of the entire surface. Such an analysis is claimed to enable analysis of alterations on a joint surface with greater accuracy than had been previously achieved. Reports of variation in structural and biomechanical properties by site within a joint (9,51) indicate the importance of sampling across the entire joint articular surface and of both cartilage and subchondral bone, if analysis and classification is to reveal valid data.

Regardless of the classification system used, it is vital that investigators consider the potential artifact-inducing effect of specimen preparation. Variability in samples, in the chemical composition and morphology, may change in response to preparation techniques. Motion analysis ideally should precede tissue analysis in order to properly determine how the joint is used and the distribution of loading during normal joint motion. Macroscopic or microscopic
analysis should be accompanied by biomechanical analysis, as the ability of the tissue especially in the knee to withstand loading may be more critical than its morphological appearance.

Physical therapists should apply a critical evaluative approach to the literature and ask the following questions:
- Was the sample defined?
- Were all animals/subjects/samples accounted for?
- Were controls reported? Were these different subjects or opposite joints?
- How were animals assigned to study groups?
- Were investigators, assessors masked (blinded) as to study group?
- Were tissues evaluated by one or more assessors?
- Was reliability (consistency) reported?
- Was the position of joint surfaces during investigation, tissue fixation, and sampling clearly shown?
- Was location of cartilage samples precisely described, were sites selected at random?
- Were tissue preparation artifacts controlled, discussed?

Use of a simple system, where Yes = 1, No = 0, should assist readers in critical appraisal of this literature.

**Capacity for Repair**

The ability of any tissue to exhibit the typical protective response to injury or disease, of inflammation, is strongly related to its vascularity. In joint dysfunction, synovial lining tissues invariably demonstrate a degree of inflammation while hyaline articular cartilage being avascular does not. Recall that a histological criterion for abnormal mature articular cartilage is the presence of blood vessels crossing the tidemark (64). With inflammation, there is cellular infiltration which, in acutely inflamed tissues, is dominated by polymorphonuclear leucocytes, whereas in chronic inflammation, mononuclear cells, macrophages, and lymphocytes dominate.

Neovascularization (angiogenesis) appears necessary to sustain chronic inflammation (38). Angiogenesis is the primary vascular response in chronic inflammation and provides fresh monocytes and other inflammatory cells. Fibrosis occurs in chronic inflammatory states and suppuration where a bacterial infection is present. The fibrosis phase may convert the proliferative fibro-fatty connective tissue formed in the inflammatory process into adhesions, which mature into strong scars, particularly if the part is immobilized. Such scars may result in significant joint contractures with consequent loss of mobility.

Healing with restoration of the original tissue is dependent on the intrinsic ability of the tissue to regenerate and the complexity of the tissue. As true regeneration does not occur in articular cartilage, there is replacement by fibrous tissue which organizes into a firm scar and frequently lacks the important characteristics of articular cartilage. Hyaline articular cartilage has a very limited and imperfect repair mechanism, particularly where the defect only involves articular cartilage and does not extend into the subchondral bone plate (58,96). The isolated living chondrocyte is not, as formerly thought, an effete cell. Chondrocytes constantly change shape, put out, and withdraw pseudopod processes. If in vitro cells from the superficial layer are transplanted to a deeper layer, they will change their shape and become more rounded (99).

Bone, a tissue with high regenerative capacity, is very responsive to stress, as from a change in loading conditions. With progressive damage to articular cartilage and exposure of collagen fibers, there is altered loading on the subchondral bone which responds by remodeling. This may result in thickening (sclerosis) of trabeculae and in the formation of spurs (osteophytes) as seen in osteoarthritis. These bony changes are enhanced by degradation of articular cartilage or detachment of cartilage secondary to its splitting. Osteophytes may provide a buttress effect, an attempt by the body to limit further excessive loading of damaged cartilage.

The complex processes involved in cartilage metabolism are dependent on many factors, including normal cartilage nutrition in which motion and loading play a vital role. There is no apparent difference in repair capacity of different levels of articular cartilage, that is, superficial or deep levels; only defects involving the subchondral plate may show repair with articular cartilage-like tissue.

The subsynovial microvasculature and lymphatics play a large role in cartilage nutrition, providing nutrients and the normal clearance mechanism vital for repair to occur. Effusion signifies imbalance between microvascular permeability, especially to proteins, and the normal clearance mechanism of the lymphatic outflow and is shown by increased protein concentration in synovial fluid. Effusion is common when inflammatory processes involve joint tissues. Damaged tissues, particularly synovial lining tissues, are infiltrated with leucocytes; there is an influx of neutrophils via increased blood flow and time-related chemo-attractants. Neutrophils can cause further damage secondary to release of proteolytic enzymes and O2-free radicals. Platelets release protease inhibitors which serve to limit tissue damage. It should be recognized that both chondrocytes and synoviocytes can produce degradative enzymes. A vicious cycle is initiated where the reaction may cause further damage.

Regular motion may adequately clear the leaking protein but rest, sleep, or immobilization allows the synovial lining tissues to become edematous; the individual experiences pain and stiffness. Even a once daily movement through the available range appears to be important in ef-
fused joints, although well-designed studies remain to be conducted.

As a result of matrix degradation, basic fibroblast growth factor and transforming growth factor-β (TGF-β) normally bound to matrix proteoglycans are released. Such extracellular messenger proteins are involved both in tissue degradation and synthesis repair. The degradative effects of interleukin-1 can be controlled by the insulin-like growth factor and TGF-β, which can stimulate collagen transcription and induce synthesis by connective tissue cells of tissue inhibiting metalloproteases and plasminogen activator 1. Insulin-like growth factors (I and II) can stimulate chondrocyte mitotic activity and proteoglycan and collagen synthesis. Fibroblastic growth factors also can stimulate chondrocyte mitotic activity.

Repair Enhancement

In the last three decades, there have been a number of histological, biochemical, biomechanical studies, as well as analytical models, that have documented the response of articular cartilage and/or chondrocytes, both in vitro and in vivo, to mechanical stimuli. This section on repair enhancement of articular cartilage will focus on studies with implications to physical therapy practice; other approaches such as grafting and implantation will be covered in other papers in this special issue. Regrettably, there are few studies reported on the direct effect of physical therapy intervention; however, studies in which exercise was employed with animal models have implications for physical therapy and training.

Exercise/Training Exercise/motion in animals and humans has been shown to cause a swelling of articular cartilage. Prolonged exercise in animals was observed to produce positive effects, such as hypertrophy of chondrocytes, an increase in the pericellular matrix, and an increase in the number of cells per chondron, particularly in the radial and transitional zones (34). In rabbits, the superficial cells became more spherical and larger for a transient period after brief exercise (31). Long-term exercise or loading produced more lasting enlargement. In young rabbits given a nonstrenuous treadmill exercise program for 8 weeks, there was an increase in the volume of nuclei but not in the overall size of the cells in the superficial layers. There also was an increase in the quantity of endoplasmic reticulum and other cytoplasmic organelles (79). Guinea pigs, after a running program, showed an increase in the size of chondrocytes (86). Helminen et al (47) observed an increase in the number but a decrease in both the volume and volume density of chondrocytes after "strenuous" running in beagles. Following moderate, nonstrenuous, running by young beagles, this Finnish group of workers reported a positive change in articular cartilage proteoglycans (87) and no degeneration of the surface after a 15-week period (55). Long distance running (up to 40 km/day, 5 day/week for 1 year) by dogs showed depletion of glycosaminoglycans from the superficial zone of articular cartilage and softening of articular cartilage at the same sites (9-11). Although these changes did not lead to articular cartilage breakdown, they do resemble those of early osteoarthritis. This group also has observed an increase in articular cartilage thickness, increased cell size, and improved anabolic processes following exercise training in animal models (47,55,79,102).

At this time, concisely summarizing exercise effects on articular cartilage is not a simple task due to the variable and often conflicting study outcomes. This variability relates to the age of animals studied, the time postexercise cessation that animals are sacrificed, and the analysis employed. More recently used quantitative histochemical and biochemical analyses provide more detail of effects, especially at the cellular level. The intensity of training affects the end result. Moderately strenuous exercise can be tolerated and may produce positive cellular changes without evident degenerative changes. Study outcomes strongly suggest that loading is more important than motion in the maintenance of cartilage properties.

It now should be obvious that we do not yet know which type of training best improves the ability of articular cartilage to withstand stress and that positively contributes to repair of articular cartilage. Exercise is shown to increase blood flow and perfusion of soft tissues in the canine wrist and knee; however, effects on cartilage are unclear (69). Such data support the use of only minimal activity to preserve range of motion and muscle balance in the acutely inflamed joint and also support the value of vigorous exercise in chronic inflamed joints.

While cells of healthy articular cartilage appear to have suppression or loss of the ability to replicate their DNA, when degeneration occurs, as in the early stages of osteoarthritis, chondrocytes appear to recover their ability to divide (45,103). Overall, repair by surviving cells seems absent when a cleft involves only articular cartilage, not subchondral bone. Salter et al (89), over the past two decades, have demonstrated healing of full thickness drill hole defects and free intra-articular periosteal grafts with continuous passive motion with hyaline-like tissue. Results have been less impressive in mature animals. It is not established how newly synthesized articular cartilage responds to normal loading over time. The evidence, however, is that physical signals, such as motion and load, are important in facilitating cartilage repair processes, however imperfect these may be. Data from animal studies also suggest that intermittent rather than continuous mechanical stress induces beneficial metabolic changes in chondrocytes, and absence of motion is detrimental.
Approaches to facilitate repair

Hyaline articular cartilage is a unique and marvelous tissue which humans have yet been able to replicate. Methods explored to improve repair are biomechanical, biophysical, involve subchondral bone, grafting, surgical implantation, and a combination of these various methods. In this paper, only those that may be a component of physical therapy management will be addressed. Investigators continue to search for methods to stimulate repair of damaged cartilage and provide a near normal articulating surface, with some of these methods being employed surgically. If techniques can be employed to simulate the coverage of the load-bearing surfaces with a tissue that has loading characteristics which permit functioning similar to natural articular cartilage, replacement procedures can be deferred. These procedures have a limited tolerance for heavy loading and vigorous wear over the long term. Delay until after maturity is especially important in young patients.

Biomechanical  Variable success from the following biomechanical approaches has been achieved: 1) decreasing the load through the weight-bearing surfaces by use of different ambulatory aids (canes, crutches); 2) use of continuous or intermittent passive motion.

Of particular interest to physical therapists should be the biomechanical approach of continuous passive motion reported mainly by Salter and associates (89). Continuous passive motion may be either continuous or cyclic. In adolescent rabbits, Salter and Field (90) demonstrated the healing of full-thickness drill hole defects by hyaline cartilage within 4 weeks, with a significant difference in the animals that had been treated by continuous passive motion. The percentage of articular cartilage in the three experimental groups of rabbits was: immobilized 8%, free motion 9%, and continuous passive motion 52%. O’Driscoll and Salter had similar results using free intra-articular periosteal grafts (72). These results were less impressive in mature rabbits. The response of the newly synthesized articular cartilage to normal loading over time was not established. Both of these studies showed a combination of approaches, continuous passive motion and involvement of the subchondral bone with the use of full thickness drill holes or periosteal grafts. Recently, simulated repair of articular cartilage matrix was reported following chemically induced osteoarthritis when intermittent active motion followed continuous passive motion (118). Future studies may show that it is the variation in the stimulus of hydrostatic pressure changes that may be more important than the motion imposed.

Coutts et al (28) demonstrated in the mediofemoral condyle of adult rabbits, with a full thickness defect and rib perichondrial grafts, that at 6 weeks nearly normal articular cartilage was present in 55% of animals, and, at 1 year, 82% demonstrated type II collagen. The shear moduli did not differ between the two groups (those exposed to cage activity alone and those having passive motion followed by cage activity). Articular cartilage with biomechanical properties developed and did not degrade within 1 year after the full thickness defects had been created. The percentage of type II collagen, the “right” type, may increase over time (6). Moran et al (71), in a rabbit model with full thickness defects and autogenous periosteal grafts, gave either continuous or intermittent passive motion. The tissue was examined with a variety of microscopy approaches and histochemistry but with no biomechanical tests. They demonstrated healing by hyaline cartilage that contained type II collagen, albeit with an irregular organization. This result was better in the animals that had been grafted and better in animals that had continuous passive motion rather than intermittent passive motion.

Regardless of the methods employed to simulate, induce, or improve repair of articular cartilage, the functional behavior of the tissue should be examined biomechanically. Microscopy studies have shown that the repair tissue may have the appearance of hyaline cartilage, but, over time, it fails to perform like articular cartilage. This suggests that an early return to sports which involves repetitive impulsive loading activities (e.g., hurdling, running, ice skating with jumps, or an occupation requiring repetitive lifting of heavy loads or incline/step climbing) is probably ill advised. A very gradual return to high loading conditions seems prudent because it has been shown in animals that the desired type II collagen takes a year or more to develop. Many professional and amateur athletes would probably balk at such a lengthy noncompetitive or low training schedule.

Biophysical  Variable effects of electromagnetic fields on cartilage and chondrocytes have been demonstrated mainly with chondrocytes grown in culture plates. No effect of pulsed electromagnetic on extracellular matrix synthesis of chondrocytes in high density cultures was observed (32). However, increased proteoglycan and DNA synthesis occurred with chondrocytes grown in cultures with constant direct current (74). Other studies also revealed a stimulating effect of electromagnetic fields on chondrocyte activity (1,2,17). Two studies have demonstrated enhanced healing of osteochondral defects in rabbits, with experimental animals showing repair tissue like hyaline cartilage (12,62). The long-term results and biomechanical characteristics of the repair tissue are not known; however, it is reasonable that electromagnetic fields should have a biological effect. Current intensity may be a critical factor. Armstrong et al (8) on growth plate chondrocytes grown in...
electrical fields showed inhibited growth with strong electrical fields but enhancement of proliferation with weaker electrical fields.

**Laser** Increased synthesis of proteoglycans and collagen was shown following exposure to CO2 and Nd:YAG-laser irradiation in organ bovine cultures and chondrocyte cultures (117). Better repair of superficial defects in guinea pig knee occurred with low-dose laser energy (25 J) compared with high-dose laser energy (125 J) and controls (91). Higher dosages (>75 J) produced cartilage and subchondral bone damage. Long-term results were not reported, and while the mechanism is unknown, the authors theorized stimulation of cell replication mechanisms. For both electromagnetic and laser therapy, more research is needed.

Many investigators have utilized a combination of different approaches, subchondral bone involvement, grafting, and/or surgical implantation. Buckwalter and Mow (21) noted the following limitations of experimental studies. If osteoarthritic joints are used, it should be remembered that the changes in osteoarthrosis are not restricted to those of articular cartilage. Regardless of the technique employed to enhance cartilage repair, it should be noted that animal models used have often been rabbits, guinea pigs, or rats, and the small joints that are used do not permit extrapolation directly to the larger joints of humans. Additionally, articular cartilage varies in thickness, cell density, composition, material properties and function between joints, and species. Further, when animal models are used, there is difficulty in assessing the long-term functional outcome. Few investigators have studied the animals for an adequate period following the experimental procedure. Pain relief, often the primary objective of intervention in humans, is difficult to assess in animals. Clinicians should be aware that “the available evidence indicates that, at a minimum, repair tissue must have initial protection from loading, followed by a regime of loading and motion that promotes remodelling (20)” but thus far experimental studies have not defined this optimal sequence of changes in the mechanical environment (21).

Clearly, it is not yet possible to give definitive directions to clinicians with regard to progression of a rehabilitative program; however, perhaps for a year, repetitive high loads, as in long distance running, should be avoided and, when used, briefly applied.

**Implications for Physical Therapy Practice**

The knowledge of the response of articular cartilage to loading and to mechanical stimuli is growing. The results of the studies over the last couple of decades appear to challenge the ancient dogma of “rest,” since in unloaded joints, rest has proven to be detrimental to the health of articular cartilage. I hypothesize that one of the objectives of physical therapy, particularly in mature clients who have been confined to bed for lengthy periods, for example, in conservative treatment of a fractured femur, should be to provide loading experiences for the unaffected leg to maintain the health of articular cartilage. This could be as simple as a regime of leg pushes against rubber bands or springs and bent-leg and resisted pelvic raises. Probably all health professionals should aim to minimize the unloaded period and, wherever possible, to allow at least partial weight bearing to provide some mechanical stimuli to the articular cartilage. Additionally, physical therapists must recognize that there is an unknown critical upper limit to the load cartilage can bear without adverse effects (Figure 4). Following injury and periods of immobility, cartilage is less stiff and less capable of tolerating high loads.

**Following injury and periods of immobility, cartilage is less stiff and less capable of tolerating high loads.**

5) cartilage deteriorates in the unloaded state, and 6) repetitive impulsive loading (eg., typing, using pneumatic drill, skipping) is detrimental to both articular cartilage and subchondral bone.

Insufficient data exist to scientifically prescribe ideal exercise programs to ensure a fluid film mechanism and avoid cartilage damage. However, prudence suggests that in the presence of joint pathology, trauma, and/or effusion, passive motion should be accompanied by gentle traction to avoid compression of softened cartilage and overstretching of vulnerable inflamed soft tissues, such as ligaments and tendons. Pendular-type movements provide a fluid film and minimal or no wear. Static loading, such as isometric exercise if
Concluded, should be very brief (a few seconds) as these conditions favor a mixed model of lubrication with boundary friction predominating. High loading should either be very brief or avoided. It is possibly least harmful following low-load, high velocity motion since these conditions favor the presence of a fluid film region. If high loads are sustained for less than 0.5 seconds, a squeeze film mechanism should ensure a fluid film exists. If resistance is applied, in any form, the individual should work through the range, and holding periods at end range (ie., knee extension) should be very brief. Controlled eccentric loading creates large compressive, ie., loading forces; these should be avoided where cartilage damage may exist.

Research suggests that cartilage has such a low permeability that any fluid flow out of cartilage to contribute to lubrication of joint surfaces is negligible. Therefore, clinicians cannot assume that load-bearing exercises will provide an adequate fluid film by promoting fluid efflux from cartilage. However, load bearing will promote fluid influx into cartilage and facilitate cartilage nutrition. It is anticipated that future research will elucidate this area for which minimal "hard" evidence currently exists and it is hoped that physical therapists will contribute to this knowledge with both basic and clinical studies. Areas to be addressed include: Are rehabilitative outcomes improved following a regime of graduated alternating load and no load exercises? Is cartilage integrity over the long term enhanced by restriction of sustained loaded conditions for a defined time period following insult? Are rehabilitative outcomes (time to return to sport/employment/length of competitive sports career) improved following a regime that excludes isometric holds and controlled eccentric exercise in the initial 3 months postinjury?

Investigators and therapists will need to follow for years, in fact, decades, patients who have pathology or therapy that either directly or indirectly jeopardizes cartilage health if the influence of different regimes is to be properly assessed; long-term longitudinal studies are required.

**CONCLUSION**

Loading appears essential to maintain healthy articular cartilage although the physiological limits of normal (safe) loading remain as yet undefined. Conditions of no load, reduced load, and excessive load are less well tolerated and often are detrimental to the health of cartilage. In therapy and training prescriptions, therapists should consider the rate, quantity, and purpose of loading.

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