ACTIVITY VS. REST IN THE TREATMENT OF BONE, SOFT TISSUE AND JOINT INJURIES

Joseph A. Buckwalter, M.D.

For at least 250 years physicians have recognized that the loading and movement of musculoskeletal tissues caused by physical activity alters these tissues and the structures they form, and may affect healing; yet the appropriate role of activity in the treatment of injuries has been a subject of controversy. Some of the most experienced and knowledgeable physicians and students of the musculoskeletal system taught that early controlled activity promotes healing and accelerates restoration of function, while others advanced the opposite view. The opponents of treatment of injuries with activity argued that absolute rest allows healing to proceed at the maximum pace, and that early use of injured musculoskeletal tissues increases inflammation and disrupts repair tissue, thereby delaying or preventing healing. A series of investigations conducted over the last several decades helped resolve this controversy thereby improving treatment of musculoskeletal injuries and defining an important area for future research.

The purpose of this paper is to clarify the roles of activity and rest in the treatment of musculoskeletal injuries. It reviews the development of the concepts of activity and rest as treatments of musculoskeletal injuries, and then compares the effects of activity, that is, loading and motion of tissues, and active muscle contraction, with the effects of rest. In particular it summarizes recent studies of cell and tissue responses to repetitive use, the specific responses of normal bone, dense fibrous tissues, cartilage and muscle to increased and decreased use, and the effects of activity on bone, soft tissue and joint healing.

ACTIVITY VS. REST

Two of the most widely recognized contributors to orthopaedics, Nicolas Andre and Julius Wolff, were among those who argued that activity benefited normal tissues. In his thesis, first presented in 1723, Nicholas Andre (1659-1742) noted that moderate exercise strengthens and shapes the musculoskeletal tissues. He advocated "action" as a more important treatment than "rest." In the latter part of the 19th century, Julius Wolff (1836-1902) described the ability of bone to adapt to changes in repetitive loading, and stressed that the adaptation of bone to changes in use occurred "according to mathematical law."

At approximately the same time, a French Orthopaedist, Just Lucas-Championniere (1843-1913) [Figure 1], went beyond the concepts of Andre and Wolff to argue that activity benefited injured tissues. He taught that movement accelerated healing, and that enforced rest injured cartilage, ligaments and muscles. He also observed that slight movement at a fracture site promoted healing rather than retarded it, and advocated massage treatment of fractures and joint injuries.

Given the observations and recommendations of Lucas-Championniere it is reasonable to ask why physicians have not included early controlled activity as a critical part of the treatment of musculoskeletal injuries for at least 100 years, and why more effort has not been directed towards investigating the effects of activity on healing of the musculoskeletal tissues and refining the clinical application of controlled activity to the treatment of injuries. The answers to these questions lie to some extent in the widely accepted teachings of a talented and influential group of investigators and physicians from Great Britain. In the 1700s John Hunter (1728-1793) prescribed "rest" as the routine treatment of "disablements" of the human motor system, a practice that John Hilton (1807-1878) strongly supported in the 1800s. Hilton considered long continuous rest the most powerful treatment a surgeon

Figure 1. Just Lucas-Championniere (1843-1913), French Orthopaedist who advocated treatment of musculoskeletal injuries with activity and taught that enforced rest damaged normal tissues.

Correspondence to: Joseph A. Buckwalter, M.D., 1201 Carver, University of Iowa, Department of Orthopaedics, Iowa City, IA 52242, Telephone (319) 356-2595

could bring to the aid of "disordered tissues," and noted that he had never seen long-continued rest produce harm. Despite the fame and influence of Hunter and Hilton, Hugh Owen Thomas (1834-1878) [Figure 2], during his long and successful career in Liverpool, became the strongest and most effective advocate of rest as the optimal treatment of musculoskeletal injuries. He believed that the only way a surgeon could promote healing was by giving an injured part rest, and that an overdose of rest was impossible. He taught that rest must be "enforced, uninterrupted, and prolonged," and observed that forced early motion stimulated inflammation that led to adhesions. The contrasting teachings of Hugh Owen Thomas and Just Lucas-Championniere show why clinical experience alone cannot form a sound foundation for a comprehensive approach to treatment of injuries or diseases. Both individuals were observant, experienced clinicians, but because they had limited information concerning the structure, composition and function of the musculoskeletal tissues and the healing of these tissues, they could not study the responses of the tissues to rest or activity, and they had limited ability to measure the outcomes of treatment and conduct controlled clinical investigations. For these reasons, clarification of the role of activity vs. rest in the treatment of injuries awaited advances in the studies of the musculoskeletal tissues.

Figure 2. Hugh Owen Thomas (1834-1891), Orthopaedist from Liverpool who taught that musculoskeletal injuries should be treated by prolonged enforced rest.

MECHANISMS OF TISSUE RESPONSE TO REPETITIVE LOADING AND MOTION

Most investigations of the effects of repetitive loading and motion focus on isolated tissues and cells, yet activity also has transient and persistent systemic effects including alterations in cardiovascular function, tissue perfusion, metabolism, and hormonal balance[30, 65, 75, 89, 101, 127, 145]. Although the influence of these systemic changes on local tissue responses to repetitive loading has not been extensively studied, they may influence the local response of tissues to repetitive use, possibly by altering the sensitivity of the tissues to cyclical loads. For this reason predicting the effects of activity on tissues in vivo from studies of the effects of loading and motion on cells and tissues in vitro must be done with caution. Nonetheless in vitro investigations provide insight into the mechanisms of the tissue responses to activity.

Recent studies of local effects of repetitive loading have identified a variety of cell and tissue responses. They have shown that repetitive loading of various types and intensities influences cell shape and cell synthetic and proliferative functions[13, 19, 22, 39, 40, 81, 114, 129]. Furthermore, they show that loading alters the alignment of the matrix macromolecules[57, 99, 12], that the matrix transmits loads to cells, and that cells can realign the matrix macromolecules in response to these loads[58, 81, 99]. The response of the tissues to loading varies among tissues and may vary with age[29, 120, 149], that is, tissues from skeletally immature individuals may be more responsive to increased use than tissues from older individuals.

The local mechanism of bone, tendon, ligament and cartilage response to loading consists of cells detecting tissue strains and responding by modifying the tissue. Experimental studies show that cells may detect tissue strain either directly through deformation of the cells, or indirectly through alterations in the matrix due to deformation of the tissue. Cyclic stretching or compression of mesenchymal cells can align intracellular microfilaments along the axis of tension, change cell shape[7, 83] and alter synthesis of DNA, matrix molecules and prostaglandins[19, 56, 60, 61, 90, 103, 110, 122, 129, 161]. Deformation of the matrix can alter matrix macromolecular organization, fluid flow, streaming currents, pressure gradients or electrical fields. These matrix alterations can influence cell function[56, 59, 96, 103]. By altering matrix macromolecular organization, matrix deformation may provide tissues with a mechanism of recording and averaging transient strains thereby giving the cells a more

sustained and coherent stimulus[128]. Loading of a tissue also can affect local vascular perfusion and diffusion through the matrix thereby altering the flow of nutrients and metabolites[15].

The local mechanisms of skeletal muscle response to changes in activity differ from those of connective tissues: dense fibrous tissue, bone and cartilage[20, 33, 44, 133]. The connective tissues consist primarily of mesenchymal cells and an extracellular matrix, while skeletal muscle consists of two components: an elaborate extracellular matrix synthesized and maintained by connective tissue cells like those found in fibrous tissues, and innervated muscle cells or myofibers[24]. The connective tissue component of skeletal muscle has a critical structural role in maintaining the tissue organization and stability[33]. In addition it contributes to the passive mechanical properties of muscle including resisting excessive elongation of the myofibers[116]. Both myofibers and muscle connective tissue cells respond to changes in muscle activity and injury. Presumably, the muscle connective tissue cells, like the cells in dense fibrous tissues, respond to changes in tissue loading and motion with alterations in cell proliferation and synthetic activity that change the organization, composition and mechanical properties of the extracellular matrix. Unlike the connective tissue cells, myofibers respond to persistent changes in the activity primarily with changes in cell structure, volume and function. The mechanisms of their response to activity remain unclear, but it appears that they respond to both stretching and repetitive active contraction.

RESPONSES OF SPECIFIC TISSUES

Studies of individual tissues show that maintenance of normal bone, dense fibrous tissue, cartilage and muscle require a minimal level of repetitive use. This minimal level varies among tissues and individuals, but activity below this level adversely alters the tissues and can eventually cause irreversible changes. The intensity and frequency of activity above the minimal level necessary to cause an adaptive tissue response also varies among tissues and individuals. In general the tissues of younger individuals appear to be more responsive. Bone and skeletal muscle have more dramatic and obvious responses to increased and decreased use, but the dense fibrous tissues and cartilage can also respond to changes in level of activity. Activity also influences healing of these tissues, but the effects vary considerably and in general remain less well understood than the effects of activity on normal tissues.

Bone

Decreased Use of Normal Bone

Immobilizing a limb in a cast or placing a patient in skeletal traction for a prolonged period of time causes bone resorption to exceed bone formation[139]. Osteoclasts resorb trabecular and cortical bone, and osteoblasts fail to replace enough bone to maintain the mass and strength of the tissue. Decreased activity may not produce readily detectable changes in bone volume, shape and strength, but prolonged immobilization of a limb will cause radiographic changes including decreased density of cancellous bone, loss of trabeculae, thinning and increased porosity of cortical bone. Regular contraction of the muscles of an immobilized limb may decrease the loss of bone[31]; but without weight bearing, bone mass declines to less than half the normal value after 12 weeks[82,139]. These alterations decrease bone strength and increase the probability of fracture. Regaining bone density after prolonged decreased use, even with vigorous activity, can require many months, even in children. In some individuals, especially older people, bone density may never return to its previous level.

Increased Use of Normal Bone

Persistent increases in cyclic loading of bone cause bone formation to exceed bone removal and can result in dramatic increases in bone density, volume and strength. In 1864, Sedillot found that removing the tibial diaphysis in dogs caused the fibula to increase in size sufficiently to compensate for the loss of the tibia[100]. A more recent study of pigs provided an equally dramatic example of the ability of bone to adapt to increased loads[55]. Resection of the ulnar diaphysis increased the compressive strain on the radius by two to two and one-half times its normal value. This led to a rapid increase in the diameter of the radius such that within three months the cross sectional bone area of the radius approached the value for the radius and ulna combined, and the compressive strain in the radius had decreased to nearly the normal value. Repetitive loading in vigorous physical activities can produce similar, although less impressive, effects[34, 36, 37, 88, 102]. For example, professional tennis players develop increased bone density, cross sectional area and diaphyseal diameter in the humerus of their dominant arm[36, 71].

Use of Injured Bone

Although fractures heal in rigidly immobilized unloaded limbs, optimal fracture healing appears to require at least some cyclical loading of the repair tissue. Loading a fracture site stimulates bone formation while decreased loading slows fracture healing[106, 126]. Limb denervation also can retard fracture healing, possibly by diminishing loading of the fracture or by inhibiting the effect of growth factors that require activation by neurotransmitters[117]. In contrast, exercise can increase the rate of repair[64], possibly through loading of the fracture. Experimental work, in particular the investigations of Kenwright, Goodship and colleagues, shows that early or almost immediate loading and movement, including induced micromotion at

long bone fracture sites, may promote fracture healing[54, 76-79], observations that support Lucas-Championniere's teachings. Clinical studies also show that early or even immediate controlled loading of long bone fractures does not impair, and may promote, fracture healing[38, 97, 125].

Dense Fibrous Tissues (Tendon, Ligament and Joint Capsule)

Decreased Use of Normal Dense Fibrous Tissue

Decreased loading of dense fibrous tissues that normally resist tension (tendon, ligament and joint capsule) alters matrix turnover so that with time, matrix degradation exceeds formation, the newly synthesized matrix is less well organized, and tissue stiffness and strength decline. Specifically prolonged limb immobilization decreases the glycosaminoglycan and water content and the degree of orientation of the matrix collagen fibrils, and may increase collagen cross linking and decrease collagen mass of the dense fibrous tissues[1-4, 6, 9-11, 148, 154, 156, 160]. The duration of decreased loading necessary to produce significant changes probably varies among tissues and individuals, but most studies show marked alterations of the tissues after six weeks of immobilization. However, in one study of rabbit patellar tendons, only three weeks of stress shielding decreased tendon tensile strength to nine percent of the control value[160].

The degree of decreased loading and motion necessary to cause these changes also remains uncertain, but one study indicates that dense fibrous tissues may be less sensitive to decreased activity than bone. Allowing active joint motion in dogs while preventing weight bearing for eight weeks decreased bone density, but did not cause resorption or weakening of the knee ligaments[82]. These results suggest that maintenance of bone structure and mechanical properties requires weight bearing, but loading due to active joint motion may be sufficient to maintain the composition and mechanical properties of the periarticular dense fibrous tissues at least for two months.

Decreased loading also alters ligament, and presumably tendon and capsular insertions into bone[26, 105, 152, 154]. The extent and severity of the alterations depend to some extent on the type of insertion. In some tendon, ligament, or joint capsule insertions (called direct insertions) most collagen fibrils pass directly into the bone matrix through a series of well defined zones that include the substance of the tendon, ligament or joint capsule, a zone of fibrocartilage, a zone of calcified cartilage and the bone[152]. In other insertions (called indirect or periosteal insertions), many of the collagen fibrils join the periosteum and relatively few fibrils pass obliquely into the bone matrix[152]. The cruciate ligament tibial and femoral insertions provide examples of direct insertions, and the tibial insertion of the medial collateral ligament provides an example of a periosteal insertion. Decreased ligament loading due to immobilization usually produces more extensive change in the periosteal type of insertion. In these types of insertions, subperiosteal osteoclasts resorb much of the bony insertion of ligaments subjected to prolonged immobilization. This leaves the ligament attached primarily to periosteum. In the direct type of insertion, resorption occurs around the insertion but relatively little resorptive activity occurs within the insertion.

The cruciate and medial collateral ligaments of the knee provide examples of the difference in the response of direct and indirect insertions to immobilization. Prolonged immobilization causes bone resorption around the periphery of the cruciate ligament insertions, but only limited resorptive activity beneath the insertion site and in the zone of mineralized fibrocartilage[104, 105]. In contrast, prolonged immobilization causes significant diffuse resorption of the bony part of tibial insertion of the medial collateral ligament[85, 152, 154]. These changes, particularly those in the periosteal type insertions, weaken the bone ligament junction significantly within six to eight weeks.

Following resumption of normal joint use, cells in the insertion site begin to form new bone and restore the structure and mechanical properties of the insertions toward normal, but complete restoration of the insertion site structure and strength following six to eight weeks of immobilization requires a longer period of active loading[9, 159]. Six to eight weeks of activity following immobilization of dog knees left ligament insertions significantly weaker than normal insertions, and the available evidence suggests that complete restoration of normal ligament insertion structure and mechanical properties requires up to one year of activity[85, 105, 154]. Muscle contractions alone probably will not prevent the changes due to decreased ligament loading since in one experiment isotonic exercises during immobilization did not prevent weakening of ligament insertions[105].

Increased Use of Normal Dense Fibrous Tissues

Experimental studies show that repetitive exercise can increase the strength, size, matrix organization and possibly collagen content of tendons, ligaments and their insertions into bone[1, 9, 25, 26, 96, 99, 135-137, 141-144, 153, 157, 159, 162, 163]. Application of tension to cultured tendons increased protein and DNA synthesis[129], and an in vivo study showed that increased loading alone can cause adaptation of dense fibrous tissue[159]. Insertion of a pin underneath rabbit medial collateral ligaments increased the load on the ligaments by 200 to 350%, and over 12 weeks significantly increased the strength of the bone ligament complex.

Aging decreases ligament stiffness and strength and may decrease the adaptive response to repetitive loading[29]. In one experiment a life long training program did not improve the mechanical properties of canine medial

collateral ligaments or flexor tendons or prevent age related deterioration of the dense fibrous tissue mechanical properties[149]. From this work it appears that age related changes in ligaments may eventually negate the potential benefits of training.

Dense fibrous tissues respond not only to changes in intensity and frequency of loading but to changes in the type of loading. Tendon regions regularly subjected to tension during normal activities differ from regions regularly subjected to compression in terms of tissue structure, matrix composition and cell synthetic activity[8, 51, 95]. Tendon regions subjected primarily to tension consist of linearly arranged dense collagen fibrils and elongated cells and have a lower proteoglycan content, different proportions of proteoglycan types and a higher rate of collagen synthesis than regions subjected to compression as well as tension[51, 84, 95, 146, 147]. Tendon regions subjected primarily to compression consist of a network of collagen fibrils separated by a proteoglycan containing matrix and more rounded cells than those found in tension bearing regions; and the cells of these regions synthesize larger proteoglycans than the cells of the regions subjected primarily to tension[95]. These differences may be caused, at least in part, by differences in the type of loading[52]. Subjecting tendons to compression increased the hyaluronic acid and chondroitin sulfate content while applying tension to the same tendon decreased the glycosaminoglycan content[51]. Like tendons, ligaments vary in thickness, matrix composition and water content among different ligaments and among regions of the same ligament[47]. Presumably, some of these variations result from adaptation to differences in loading.

Use of Injured Dense Fibrous Tissue

Experimental work shows that controlled loading applied at the optimal time during repair of dense fibrous tissue injuries can promote healing[11, 25, 26, 32, 46, 49, 50, 67, 115, 135-137, 140, 155, 158]. Tensile loading of tendon repair tissue appears to cause the repair cells and matrix collagen fibrils to line up parallel to the axis of tension[13, 16]. Lack of tension leaves the repair tissue cells and fibers disoriented. Loading may also alter the rate of tendon repair[49]. Three weeks following injury, surgically repaired tendons treated with early mobilization had twice the strength of repaired tendons treated with immobilization[50]. Twelve weeks following injury, repaired tendons treated with early mobilization had greater strength than repaired tendons treated with an initial period of immobilization. Controlled loading and motion soon after injury can accelerate ligament repair by increasing the wet and dry weight of injured ligaments, improving matrix organization and inducing more rapid return of normal tissue DNA content, collagen synthesis and strength[11, 48, 92, 140].

Excessive or uncontrolled loading of injured tissues disrupts repair tissue, causes further damage and may delay or prevent repair. In a study of medial collateral ligament healing in rats, forced exercise increased the strength of ligament repair tissue in stable knees[32]. In unstable knees, forced exercise did not increase the stiffness and strength of the repair tissue but increased joint instability. Another study of the effects of anterior cruciate ligament transection showed that temporary immobilization of the knee prevented the development of osteophytes suggesting that early motion following injury may have increased the joint instability[111]. For this reason loading and motion treatment of dense fibrous tissue injuries must be carefully controlled. Furthermore, the optimal motion and loading treatment probably differs among the types of dense fibrous tissues, the types of injuries and among patients. For example, the optimal timing and intensity of loading and motion treatment of a clean laceration of a digital extensor tendon in a child may differ from the optimal loading and motion treatment of a crushing muscle-tendon avulsion of the Achilles tendon in an adult.

Articular Cartilage

Decreased Use of Normal Articular Cartilage

Persistent decreases in loading and motion of a synovial joint cause articular cartilage changes that parallel the changes in the periarticular dense fibrous tissues: chondrocytes change their synthetic activity, cartilage proteoglycan concentration decreases, matrix organization may decrease and the mechanical properties deteriorate[17, 18, 28, 42, 43, 45, 53, 62, 63, 66, 72, 74, 80, 108, 109, 113, 118, 119, 121, 130, 131, 134, 138]. Although loading of an immobilized joint by repetitive muscle contraction may help preserve the cartilage[31], the maintenance of normal synovial joint structure, composition and function requires both loading and motion[112].

Cartilage alterations occur soon after a persistent decrease in joint use. Forty days following experimental tibia fractures in dogs the articular cartilage of the operated limb had a significantly lower glycosaminoglycan concentration[108]. Presumably the decrease in glycosaminoglycan concentration resulted from decreased loading and motion of the joints due to the fracture. Cast immobilization of a dog limb also damaged articular cartilage[74, 80, 109, 113]. Six weeks or more of cast immobilization decreased cartilage thickness, uronic acid content and proteoglycan synthesis and diminished the ability of proteoglycans to form aggregates. Cessation of immobilization followed by ambulation in a pen for three weeks reversed the changes. Treadmill exercise after cessation of immobilization prevented the reversal indicating that intense and frequent loading of the damaged cartilage impeded repair[109].

A study comparing the effects of six weeks of immobilization of dog knees using external fixators with the effects of six weeks of immobilization in long leg casts suggests that the rigidity of joint immobilization influences the severity of the joint damage[18]. External fixators rigidly immobilized the knees, but long leg cast immobilization allowed eight to 15 degrees of motion. Cartilage water content increased 7% in both groups of knees, but hexouronate concentration decreased 23% in the joints treated with casts and 28% in the joints immobilized by rigid external fixators. The rigid fixators also produced more severe depression of proteoglycan synthesis and proteoglycan loss, and impaired cartilage recovery. Within a week after remobilization, joints treated with long leg casts had recovered near normal hexouronate content, but rigidly immobilized joints showed little or no evidence of recovery of hexouronate content.

Continued immobilization of joints eventually causes irreversible damage including contracture of periarticular dense fibrous tissues and muscles that act across the joint, loss of articular cartilage and obliteration of the joint cavity by fibrofatty tissue[42, 45]. Once the fibrofatty tissue fills the joint, attempts to forcefully restore motion tear the intra-articular tissue, often in a different plane than that of the original joint cavity, and avulse fragments of remaining articular cartilage[42, 43].

The time of immobilization necessary to irreversibly damage a synovial joint probably varies among joints and species. Most animal studies suggest that controlled remobilization can reverse the damage caused by a month or more of immobilization. In rat joints, remobilization reversed changes due to 30 days of immobilization, but 60 days of immobilization caused irreversible changes[43]. Two weeks of immobilization of rabbit knees did not cause any detectable permanent changes, but after six weeks some joints had developed contractures[45]. In dog knees, six days of immobilization decreased proteoglycan synthesis 41% and three weeks of immobilization caused loss of proteoglycan aggregation. Two weeks of active motion restored proteoglycan aggregation to normal[113]. Another study of dog joints showed that 15 weeks of remobilization improved but did not completely restore the mechanical properties of dog articular cartilage subjected to 11 weeks of cast immobilization[74].

Increased Use of Normal Articular Cartilage

Increased loading and motion of articular cartilage, up to a certain level, may increase matrix synthesis relative to matrix degradation, at least in skeletally immature animals. In one series of investigations the effects of regular running in dogs depended on the distance the animals ran. Moderate running (four kilometers/day five days a week for 40 weeks) increased cartilage thickness, proteoglycan content and indentation stiffness[50, 111, 144, 162, 163]. A period of more strenuous running (20 kilometers/day five days a week for 15 weeks) decreased cartilage thickness and proteoglycan content[91, 111, 149]. Longer term low-impact strenuous running (40 kilometers/day for up to one year) decreased cartilage proteoglycan concentration and indentation stiffness and stimulated remodeling of subchondral bone, but these animals did not develop degenerative joint disease[14, 107]. These studies suggest that a limited period of increased use may alter articular cartilage composition and mechanical properties, but it does not accelerate joint degeneration. They also suggest that synovial joint tissues, especially in skeletally immature individuals, may be able to adapt to increased use.

Use of Injured Articular Cartilage

The effects of early loading and motion on injured cartilage vary with the type of cartilage injury[23, 25, 28]. Differences in the type of tissue damage and the repair response separate acute cartilage injuries into three types[23, 25, 28]: 1) loss or abnormalities of the matrix macromolecules without disruption of the tissue; 2) disruption of cartilage without injury to subchondral bone; 3) disruption of cartilage and subchondral bone. Chondrocytes can restore lost proteoglycans if the collagen matrix of articular cartilage remains intact and if enough chondrocytes remain viable. Chondrocytes cannot repair disruptions of the tissue like chondral fractures or cartilage lacerations. Following cartilage injury they briefly increase their synthetic and proliferative activity, but they do not migrate to the site of injury or produce new cells and matrix that fill the tissue defect. Disruption of subchondral bone along with cartilage causes hemorrhage and initiates inflammation and repair by cells from the bone and the bone blood vessels. A fibrin clot forms in the tissue defect. Mesenchymal cells migrate into the clot and produce repair tissue that usually fills the bone defect and most of the chondral defect. The cells in the chondral portion of the defect then produce repair tissue that usually has a matrix with a composition intermediate between fibrocartilage and articular cartilage[23, 25, 28].

The available evidence indicates that controlled early movement prevents cartilage degeneration following joint injury and may facilitate healing. The observations that prolonged joint immobilization and unloading injure articular cartilage, that cyclic loading increases chondrocyte synthetic activity and that resumption of use following joint immobilization improves articular cartilage composition and mechanical properties suggest that controlled loading and motion may stimulate repair of cartilage damage limited to loss of matrix proteoglycans. Furthermore, in one study active and passive motion following experimental depletion of proteoglycans stimulated restoration of matrix proteoglycans[151], but there is no evidence that joint use promotes repair of injuries that disrupt the cartilage

without damaging subchondral bone. Early motion during the repair and remodeling phases of healing following osteochondral injuries can decrease or prevent adhesions and immobilization-induced deterioration of uninjured cartilage, and studies of the effects of early passive motion treatment on experimental osteochondral injuries indicate that passive motion improves the initial quality of cartilage repair tissue[123, 124].

Despite the necessity of loading and motion for maintenance of articular cartilage, premature or excessive loading and motion may delay healing or disrupt cartilage repair tissue[5, 25, 28, 109, 150]. Following injuries associated with depletion of matrix proteoglycans, repetitive intense loading of cartilage, especially impact loading, before the chondrocytes restore the matrix proteoglycan content, may cause further damage[25, 27]. Guinea pig knees subjected to chemical injury developed cartilage fibrillation and osteophytes after three weeks of unrestrained active joint use; immobilization for three weeks prevented fibrillation and osteophyte formation[150]. Running on a treadmill for three weeks following prolonged immobilization of dog knees prevented reversal of the immobilization induced changes in cartilage proteoglycans[109]. Early loading and motion may also damage the repair tissue that forms following osteochondral injury. Examination of the effect of abrading the femoral heads of dogs showed that protection of an abraded surface from loading allowed formation of cartilage repair tissue[5]. Areas subjected to heavy loading formed little or no repair tissue.

Skeletal Muscle

Decreased Use of Normal Skeletal Muscle

Decreased use of skeletal muscle rapidly causes easily detectable changes in muscle volume, structure and function[12, 21, 35, 41, 93]. Within weeks of a reduction in frequency or intensity of activity, myofiber and myofibril volumes and oxidative capacity decrease causing decreases in muscle mass and strength. A decrease in intramuscular capillary density and an increase in intramuscular connective tissue volume relative to myofiber volume accompany these changes in the myofibers[73]. Rigid immobilization produces more rapid and severe loss of muscle structure, volume and function than a decrease in the frequency or intensity of activity. Muscle protein synthesis decreases within six hours of cast immobilization of a limb[21]. Two weeks of cast immobilization decreases muscle fiber size and causes loss of myofibrils and with increasing length of immobilization, mitochondria enlarge, lose their cristae and disintegrate[35]. Eventually the muscle cells contain only amorphous protein, vesicles and fragments of membranes. As the myofibers degenerate, fibrous tissue and fat become a progressively larger proportion of the tissue.

Changes in muscle volume and function accompany these structural alterations. Six weeks of cast immobilization decreased the weight of cat muscles nearly 25%, and 22 weeks of cast immobilization decreased muscle weight nearly 70%[35]. The ability of these muscles to generate tension decreased as muscle weight decreased. In humans six weeks of cast immobilization for treatment of forearm fractures had a similar effect on muscle strength: adductor pollicis muscle maximal voluntary contraction decreased 55% and maximal electrically evoked contraction decreased 33%[41].

Increased Use of Normal Skeletal Muscle

Persistent increases in use also change the structure, functional capacity and often the volume of skeletal muscle[20, 94, 132, 133]. The specific adaptive changes in muscle depend on the pattern of increased use. Patterns that produce different muscle responses include[33]: low-tension high-repetition use that primarily increases muscle endurance; high-tension low-repetition use that primarily increases muscle strength; and, stretching that primarily increases muscle strength. Initially muscle may respond to a training program with rapid changes in structure and function, but as adaptation occurs, the rate of change decreases and eventually the muscle reaches a stable state.

Repetitive low-tension high-repetition exercise, like walking, running, cycling or swimming, performed for 30 to 60 minutes at a time, increases the capacity of muscle cells for sustained effort. This type of endurance training increases the number and size of muscle cell mitochondria, muscle glycogen concentration and the proportion of muscle cells identified as having high oxidative capacity[33, 98]. These changes can double the muscle oxidative capacity[33, 98]. Strength training programs usually consist of repetitive high-tension low-repetition muscle use. These programs increase muscle strength and usually volume, primarily by causing cell hypertrophy - that is, increasing the number of myofibrils. Strength training programs generally do not increase muscle oxidative capacity. Stretching accelerates muscle protein turnover and can cause hypertrophy and increase strength[33].

Use of Injured Muscle

The effects of activity on muscle healing depend to some extent on when activity begins following injury. Immediate mobilization of injured muscles may increase scar formation and interfere with orderly regeneration of myofibers[70], but mobilization following a short period of immobilization produces more rapid disappearance of the hematoma and inflammatory cells, more extensive, rapid and organized myofiber regeneration, and more rapid increase in tensile strength and stiffness[68-70, 86, 87]. In contrast, prolonged immobilization following injury produces muscle atrophy and poor organization of the regenerating myofibers[70, 86, 87]. These results suggest that after

a brief period of rest, controlled use of an injured muscle will produce the optimal healing.

SUMMARY AND CONCLUSIONS

One of the most important advances in the treatment of musculoskeletal injuries has come from understanding that controlled early resumption of activity can promote restoration of function, and that treatment of injuries with prolonged rest may delay recovery and adversely affect normal tissues. In the last decade of the nineteenth century two widely respected orthopaedists with extensive clinical experience strongly advocated opposing treatments of musculoskeletal injuries. Hugh Owen Thomas in Liverpool believed that enforced, uninterrupted prolonged rest produced the best results. He noted that movement of injured tissues increased inflammation, and that, "It would indeed be as reasonable to attempt to cure a fever patient by kicking him out of bed, as to benefit joint disease by a wriggling at the articulation." Just Lucas-Championnier in Paris took the opposite position. He argued that early controlled active motion accelerated restoration of function, although he noted that mobility had to be given in limited doses. In general, Thomas' views met with greater acceptance in the early part of this century, but experimental studies of the last several decades generally support Lucas-Championneir. They confirm and help explain the deleterious effects of prolonged rest and the beneficial effects of activity on the musculoskeletal tissues. They have shown that maintenance of normal bone, tendon and ligament, articular cartilage and muscle structure and composition require repetitive use, and that changes in the patterns of tissue loading can strengthen or weaken normal tissues. Although all the musculoskeletal tissues can respond to repetitive loading, they vary in the magnitude and type of response to specific patterns of activity. Furthermore, their responsiveness may decline with increasing age. Skeletal muscle and bone demonstrate the most apparent response to changes in activity in individuals of any age. Cartilage and dense fibrous tissues also can respond to loading, but the responses are more difficult to measure. The effects of loading on injured tissues have been less extensively studied, but the available evidence indicates that repair tissues respond to loading and, like immature normal tissues, may be more sensitive to cyclic loading and motion than mature normal tissues. However, early motion and loading of injured tissues is not without risks. Premature or excessive loading and motion of repair tissue can inhibit or stop repair. Unfortunately, the optimal methods of facilitating healing by early application of loading and motion have not been defined. Nonetheless, experimental studies and newer clinical investigations document the benefits of early controlled loading and motion in the treatment of musculoskeletal injuries, and orthopaedists should consider controlled activity as part of the optimal treatment of musculoskeletal injuries.

REFERENCES

1. Akeson, W.H.: The Response of Ligaments to Stress Modulation and Overview of the Ligament Healing Response. in Daniel, D.; Akeson, W.H.; and O'Connor, J.J., Editors: Knee Ligaments: Structure, Function, Injury, and Repair, pp. 315-327. New York: Raven Press, 1990.

2. Akeson, W.H.; Amiel, D.; and Violette, D.L.: The connective tissue response to immobility: a study of the chondroitin-4 and 6-sulfate and dermatan sulfate changes in periarticular connective tissue of control and immobilized knees of dogs. Clin Ortho Rel Res 51:183-197, 1967.

3. Akeson, W.H.; Amiel, D.; and Woo, S.L.-Y.: Immobility effects on synovial joints: the pathomechanics of joint contracture. Biorheology 17:95-110, 1980.

4. Akeson, W.H.; Amiel, E.; Mechanic, G.L.; Woo, S.L.-Y.; Harwood, F.L.; and Hammer, M.L.: Collagen cross-linking alterations in joint contractures: changes in the reducible cross-links in periarticular connective tissue collagen after nine weeks of immobilization. Conn Tissue Res 5:15-19, 1977.

5. Akeson, W.H.; Miyashita, C.; Taylor, T.K; et al.: Experimental cup arthroplasty of the canine hip. J Bone Joint Surg 51-A:149-164, 1969.

6. Akeson, W.H.; Woo, S.L.-Y.; Amiel, D.; Coutts, R.D.; and Daniel, D.: The connective tissue response to immobility: biochemical changes in periarticular connective tissue of the immobilized rabbit knee. Clin Ortho Rel Res 93:356-362, 1973.

7. Albrecht-Buehler, G.: Role of cortical tension in fibroblast shape and movement. Cell Motility Cyto 7:54-67, 1987.

8. Amadio, P.C.; Bergland, L.J.; and Ahn, K.N.: Tensile properties of biochemically discrete zones of canine flexor tendon. Trans Ortho Res Soc 14:251, 1989.

9. Amiel, D.; Schroeder, H.V.; and Akeson, W.H.: The response of ligaments to stress deprivation and stress enhancement. in Daniel, D.; Akeson, W.H.; and O'Connor, J.J., Editors: Knee Ligaments: Structure, Function, Injury, and Repair, pp. 329-336. New York: Raven Press, 1990.

10. Amiel, D.; Woo, S.L.-Y.; Harwood, F.L.; and Akeson, W.H.: The effect of immobilization on collagen turnover in connective tissue: a biochemical-biomechanical correlation. Acta Orthop Scand 53:325-332, 1982.

11. Andriacchi, T.; Sabiston, P.; DeHaven, K.; Dahners, L.; Woo, S.; Frank, C.; Oakes, B.; Brand, R.; and Lewis, J.: Ligament: Injury and repair. in Woo, S.L.-Y.; and Buckwalter, J.A., Editors: Injury and Repair of the Mus-

culoskeletal Soft Tissues, pp. 103-128. Park Ridge, IL: American Academy of Orthopaedic Surgeons, 1988.
12. Appell, H.J.: Morphology of immobilized skeletal muscle and the effects of a pre- and post immobilization training program. Int J Sports Med 7:6-12, 1986.
13. Arem, A.J.; and Madden, J.W.: Effects of stress on healing wounds: I. Intermittent noncyclical tension. J Surg Res 20:93-102, 1976.
14. Arokoski, J.; Kiviranta, I.; Jurvelin, J.; Tammi, M.; and Helminen, H.J.: Long-distance running causes site-dependent decrease of cartilage glycosaminoglycan content in the knee joints of beagle dogs. Arth Rheum 36:1451-1459, 1993.
15. Bader, D.L.; Barnhill, R.L.; and Ryan, T.J.: Effect of externally applied skin surface forces on tissue vasculature. Arch Phys Med Rehabil 67:807-811, 1986.
16. Bair, G.R.: The effect of early mobilization versus casting on anterior cruciate ligament reconstruction. Trans 26th Ann Mtg Ortho Res Soc 5:108, 1980.
17. Baker, W.C.; Thomas, T.G.; and Kirkaldy-Willis, W.H.: Changes in the cartilage of the posterior intervertebral joints after anterior fusion. J Bone Joint Surg 51-B:736-746, 1969.
18. Behrens, F.; Kraft, E.L.; and Oegema, T.R.: Biochemical changes in articular cartilage after joint immobilization by casting or external fixation. J Ortho Res 7:335-343, 1989.
19. Binderman, I.; Shimshoni, Z.; and Somjen, D.: Biochemical pathways involved in the translation of physical stimulus into biological message. Calcif Tissue Int 36:S82-S85, 1984.
20. Booth, F.W.: Perspectives on molecular and cellular exercise physiology. J Appl Physiol 65:1461-1471, 1988.
21. Booth, F.W.: Physiologic and biochemical effects of immobilization on muscle. Clin Orthop 219:15-20, 1987.
22. Brunette, D.M.: Mechanical stretching increases the number of epithelial cells synthesizing DNA in culture. J Cell Sci 69:35-45, 1984.
23. Buckwalter, J.A.: Mechanical Injuries of Articular Cartilage. in Finerman, G., Editor: Biology and Biomechanics of the Traumatized Synovial Joint, pp. 83-96. Park Ridge IL: American Academy of Orthopaedic Surgeons, 1992.
24. Buckwalter, J.A.: Musculoskeletal Tissues and the Musculoskeletal System. in Weinstein, S.L.; and Buckwalter, J.A., Editors: Turek's Orthopaedics: Principles and Their Application, pp. 13-67. Philadelphia: Lippincott, 1994.
25. Buckwalter, J.A.; and Cruess, R.: Healing of musculoskeletal tissues. in Rockwood, C.A.; and Green, D., Editors: Fractures, : Lippincott, 1991.
26. Buckwalter, J.A.; Maynard, J.A.; and Vailas, A.C.: Skeletal fibrous tissues: tendon, joint capsule, and ligament. in Albright, J.A.; and Brand, R.A., Editors: The Scientific Basis of Orthopaedics, pp. 387-405. Norwalk: Appleton & Lange, 1987.
27. Buckwalter, J.A.; and Mow, V.C.: Cartilage Repair in Osteoarthritis. in Moskowitz, R.W., et al., Editors: Osteoarthritis: Diagnosis and Management 2nd edition, pp. 71-107. Philadelphia: Saunders, 1992.
28. Buckwalter, J.A.; Rosenberg, L.C.; and Hunziker, E.: Articular cartilage: composition, structure, response to injury and methods of facilitating repair. in Ewing, J.W., Editor: The Science of Arthroscopy, pp. 19-56. New York: Raven Press, 1990.
29. Buckwalter, J.A.; Woo, S.-L.Y.; Goldberg, V.M.; Hadley, E.C.; Booth, R.; Oegema, T.R.; and Eyre, D.R.: Soft tissue aging and musculoskeletal function. J Bone Joint Surg 75A:1533-1548, 1993.
30. Bunt, J.C.: Hormonal alterations due to exercise. Sports Med 3(5):331-345, 1986.
31. Burr, D.B.; Frederickson, R.G.; Pavlinch, C.; Sickles, M.; and Burkart, S.: Intracast muscle stimulation prevents bone and cartilage deterioration in cast-immobilized rabbits. Clin Ortho Rel Res 189:264-278, 1984.
32. Burroughs, P.; and Dahners, L.E.: The effect of enforced exercise on the healing of ligament injuries. Am J Sports Med 18(4):376-378, 1990.
33. Caplan, A.; Carlson, B.; Faulkner, J.; Fishman, D.; and Garrett, W.: Skeletal Muscle. in Woo, S.L.; and Buckwalter, J.A., Editors: Injury and Repair of the Musculoskeletal Soft Tissues, pp. 213-291. Park Ridge, IL: American Academy of Orthopaedic Surgeons, 1988.
34. Carter, D.R.: Mechanical loading histories and cortical bone remodeling. Calcif Tissue Int 36(suppl):S19-S24, 1984.
35. Cooper, R.R.: Alterations during immobilization and regeneration of skeletal muscle in cats. J Bone Joint Surg 54-A:919-953, 1972.
36. Dalen, N.; Laftman, P.; Ohlsen, H.; and Stromberg, L.: The effect of athletic activity on the bone mass in human diaphyseal bone. Orthopedics 8:1139-1141, 1985.
37. Dalen, N.; and Olsson, K.E.: Bone mineral content and physical activity. Acta Orthop Scand 45:170-174, 1974.
38. Dehne, E.; Metz, C.W.; Deffer, P.A.; and Hall, R.M.: Non-operative treatment of the fractured tibia by immediate weight bearing. J Trauma 1:514-535, 1961.
39. DeWitt, M.T.; Handley, C.J.; Oakes, B.W.; and Lowther, D.A.: In vitro response of chondrocytes to mechanical loading. The effect of short term mechanical tension. Conn Tiss Res 12:97-109, 1984.
40. Dodds, R.A.; Ali, N.; Pead, M.J.; and Lanyon, L.E.: Early loading-related changes in the activity of glucose-6-phosphate dehydrogenase and alkaline phosphatase in osteocytes and periosteal osteoblasts in rat fibulae in vivo. J Bone Miner Res 8:261-267, 1993.

41. Duchateau, J.; and Hainaut, K.: Electrical and mechanical changes in immobilized human muscle. J Appl Physiol 62:2168-2173, 1987.

42. Enneking, W.F.; and Horowitz, M.: The intra-articular effects of immobilization on the human knee. J Bone Joint Surg 54-A:973-985, 1972.

43. Evans, E.B.; Eggers, G.W.N.; Butler, J.K.; and Blumel, J.: Experimental immobilization and remobilization of rat knee joints. J Bone Joint Surg 42-A:737-758, 1960.

44. Faulkner, J.A.: New perspectives in training for maximum performance. JAMA 205:741-746, 1968.

45. Finsterbush, A.; and Friedman, B.: Reversibility of joint changes produced by immobilization in rabbits. Clin Ortho Rel Res 111:290-298, 1975.

46. Frank, C.; Akeson, W.H.; Woo, S.L.-Y.; Amiel, D.; and Coutts, R.D.: Physiology and therapeutic value of passive joint motion. Clin Orthop Rel Res 185:113-125, 1984.

47. Frank, C.; McDonald, D.; Lieber, R.L.; et al.: Biochemical heterogeneity within the maturing rabbit medial collateral ligament. Clin Ortho Rel Res 236:279-285, 1988.

48. Fronek, J.; Frank, C.; Amiel, D.; et al.: The effects of intermittent passive motion (IPM) in the healing of medial collateral ligament. Trans Ortho Res Soc 8:31, 1983.

49. Gelberman, R.; Goldberg, V.; An, K.-N.; and Banes, A.: Tendon. in Woo, S.L.-Y.; and Buckwalter, J.A., Editors: Injury and Repair of the Musculoskeletal Soft Tissues, pp. 1-40. Park Ridge, IL: American Academy of Orthopaedic Surgeons, 1988.

50. Gelberman, R.H.; Woo, S.L.-Y.; Lothringer, K.; Akeson, W.H.; and Amiel, D.: Effects of early intermittent passive mobilization on healing canine flexor tendons. J Hand Surg 7(2):170-175, 1982.

51. Gillard, G.C.; Reilly, H.C.; Bell-Booth, P.G.; and Flint, M.H.: The influence of mechanical forces on the glycosaminoglycan content of the rabbit flexor digitorum profundus tendon. Conn Tiss Res 7:37-46, 1979.

52. Giori, N.J.; Beaupre, G.S.; and Carter, D.R.: Cellular shape and pressure may mediate mechanical control of tissue composition in tendons. J Orthop Res 11:581-591, 1993.

53. Good, S.C.: A study of the effects of experimental immobilization on rabbit articular cartilage. J Anat 108:497-507, 1971.

54. Goodship, A.E.; and Kenwright, J.: The influence of induced micromovement upon the healing of experimental tibial fractures. J Bone Joint Surg 67-B:650, 1985.

55. Goodship, A.E.; Lanyon, L.E.; and McFie, H.: Functional adaptation of bone to increased stress. J Bone Joint Surg 61-A:539-546, 1979.

56. Gray, M.L.; Pizzanelli, A.M.; Godzinsky, A.J.; and Lee, R.C.: Mechanical and physicochemical determinants of chondrocyte biosynthetic response. J Ortho Res 6:777-792, 1988.

57. Greco, F.; Specchia, N.; Falciglia, F.; Toesca, A.; and Nori, S.: Ultrastructural analysis of the adaptation of articular cartilage to mechanical stimulation. Intl J Orthop Traumatol 18:311-321, 1992.

58. Grinnell, F.; and Lamke, C.R.: Reorganization of hydrated collagen lattices by human skin fibroblasts. J Cell Sci 66:51-63, 1984.

59. Grodzinsky, A.J.: Electromechanical and physicochemical properties of connective tissue. CRC Reviews in Biomedical Engineering 9(2):133-199, 1983.

60. Hall, A.C.; Urban, J.P.; and Gehl, K.A.: The effects of hydrostatic pressure on matrix synthesis in articular cartilage. J Orthop Res 9:1-10, 1991.

61. Hall, A.C.; and Urban, J.P.G.: Responses of articular chondrocytes and cartilage to high hydrostatic pressure. Trans Ortho Res Soc 14:49, 1989.

62. Hall, M.C.: Cartilage changes after experimental immobilization of the knee joint of the young rat. J Bone Joint Surg 45-A:36-44, 1963.

63. Hall, M.C.: Cartilage changes after experimental relief of contact in the knee joint of the mature rat. Clin Ortho Rel Res 64:64-76, 1969.

64. Heikkinen, E.; Vihersaari, T.; and Penttinen, R.: Effect of previous exercise on fracture healing: A biochemical study with mice. Acta Orthop Scand 45:481-489, 1974.

65. Heikkinen, E.; and Vuori, I.: Effect of physical activity on the metabolism of collagen in aged mice. Acta Physiol Scand 84:543-549, 1972.

66. Helminen, H.J.; Jurvelin, J.; Kuusela, T.; Heikkila, R.; Kiviranta, I.; and Tammi, M.: Effects of immobilization for 6 weeks on rabbit knee articular surfaces as assessed by the semiquantitative steromicroscopic method. Acta Anat 115:327-335, 1983.

67. Indelicato, P.A.; Hermansdorfer, J.; and Huegel, M.: Nonoperative management of complete tears of the medial collateral ligament of the knee in intercollegiate football players. Clin Ortho Rel Res 256:174-177, 1990.

68. Jarvinen, M.: Healing of a crush injury in rat striated muscle. 4. Effect of early mobilization and immobilization of the tensile properties of gastrocnemius muscle. Acta Chir Scand 142:47-56, 1976.

69. Jarvinen, M.: Healing of crush injury in rat striated muscle. 2. Histological study of the effect of early mobilization and immobilization on the repair process. Acta Pathol Microbiol Immunol Scand 83:269-282, 1975.

70. Jarvinen, M.J.; and Lehto, M.U.: The effects of early mobilization and immobilization on the healing process following muscle injuries. Sports Med 15(2):78-89, 1993.

[71.] Jones, H.H.; Priest, J.D.; Hayes, W.C.; Tichenor, C.C.; and Nagel, D.A.: Humeral hypertrophy in response to exercise. J Bone Joint Surg 59A:204-208, 1977.

[72.] Jozsa, L.; Jarvinen, M.; Kannus, P.; and Reffy, A.: Fine structural changes in the articular cartilage of the rat's knee following short-term immobilization in various positions: a scanning electron microscopic study. Int Orthop 11:129-133, 1987.

[73.] Jozsa, L.; Kannus, P.; Thoring, J.; Reffy, A.; Jarvinen, M.; and Kvist, M.: The effect of tenotomy and immobilization on intramuscular connective tissue. A morphometric and microscopic study in rat calf muscles. J Bone Joint Surg 72B:293-297, 1990.

[74.] Jurvelin, J.; Kiviranta, I.; Saamanen, A.-M.; Tammi, M.; and Helminen, H.J.: Partial restoration of immobilization-induced softening of canine articular cartilage after remobilization of the knee (stifle) joint. J Ortho Res 7:352-358, 1989.

[75.] Keizer, H.A.; Kuipers, H.; Haan, J.D.; Janssen, G.M.; Beckers, E.; Habets, L.; Kranenburg, G.V.; and Geurten, P.: Effect of a 3-month endurance training program on metabolic and multiple hormonal responses to exercise. Int J Sports Med 8 Suppl 3:154-160, 1987.

[76.] Kenwright, J.; and Goodship, A.E.: Controlled mechanical stimulation in the treatment of tibial fractures. Clin Orthop 241:36-47, 1989.

[77.] Kenwright, J.; Richardson, J.B.; Cunningham, J.L.; White, S.H.; Goodship, A.E.; Adams, M.A.; Magnussen, P.A.; and Newman, J.H.: Axial movement and tibial fractures. a controlled randomized trial of treatment. J Bone Joint Surg 73B:654-659, 1991.

[78.] Kenwright, J.; Richardson, J.B.; Goodship, A.E.; Evans, M.; Kelly, D.J.; Spriggins, A.J.; Newman, J.H.; Burrough, S.J.; Harris, J.D.; and Rowley, D.I.: Effect of controlled axial micromovement on healing of tibial fractures. Lancet 2:1185-1187, 1986.

[79.] Kershaw, C.J.; Cunningham, J.L.; and Kenwright, J.: Tibial external fixation, weight bearing, and fracture movement. Clin Orthop 293:28-36, 1993.

[80.] Kiviranta, I.: Joint Loading Influences on the Articular Cartilage of Young Dogs. pp. 91. 1st ed. Kuopio: University of Kuopio. 1987.

[81.] Klebe, R.J.; Caldwell, H.; and Milam, S.: Cells transmit spatial information by orienting collagen fibers. Matrix 9:451-458, 1989.

[82.] Klein, L.; Heiple, K.G.; Torzilli, P.A.; Golberg, V.M.; and Burstein, A.H.: Prevention of ligament and meniscus atrophy by active joint motion in a non-weight bearing model. J Ortho Res 7:80-85, 1989.

[83.] Kolega, J.: Effects of mechanical tension on protrusive activity of and microfilament and intermediate filament organization in an epidermal epithelium moving in culture. J Cell Biol 102:1400-1411, 1986.

[84.] Koob, T.J.; and Vogel, K.G.: Proteoglycan synthesis in organ cultures from regions of tendon subjected to different mechanical forces. Biochem J 246:589-598, 1987.

[85.] Laros, G.S.; Tipton, C.M.; and Cooper, R.R.: Influence of physical activity on ligament insertions in the knees of dogs. J Bone Joint Surg 53-A:275-286, 1971.

[86.] Lehto, M.; Duance, V.C.; and Restall, D.: Collagen and fibronectin in a healing skeletal muscle injury. An immunohistochemical study of the effects of physical activity on the repair of injured gastrocnemius muscle in the rat. J Bone Joint Surg 67(5):820-828, 1985.

[87.] Lehto, M.; Jarvinen, M.; and Nelimarkka, O.: Scar formation after skeletal muscle injury. A histological and autoradiographical injury. Arch Orthop Traum Surg 104(6):366-370, 1986.

[88.] Leichter, I.; Simkin, A.; Magulies, J.Y.; Bivas, A.; Streinberg, R.; Giladi, M.; and Milgrom, C.: Gain in mass density of bone following strenuous physical activity. J Ortho Res 7:86-90, 1990.

[89.] Lenz, T.; Weiss, M.; Werle, E.; Walz, U.; Kohler, U.; Pinther, J.; and Weicker, H.: Influence of exercise in water on hormonal, metabolic and adrenergic receptor changes in man. Int J Sports Med 9 Suppl 2:125-131, 1988.

[90.] Leung, D.Y.M.; Glagov, S.; and Mathews, M.B.: A new in vitro system for studying cell response to mechanical stimulation: different effects of cyclic stretching and agitation on smooth muscle cell biosynthesis. Exp Cell Res 109:285-298, 1977.

[91.] Lewis, L.B.; and Trelstad, R.L.: Patterns of cell polarity in the developing mouse limb. Dev Biol 59:164-173, 1977.

[92.] Long, M.; Frank, C.; Schachar, N.; et al.: The effects of motion on normal and healing ligaments. Trans Ortho Res Soc 7:43, 1982.

[93.] Maeda, H.; Kimmel, D.B.; Raab, D.M.; and Lane, N.E.: Musculoskeletal recovery following hindlimb immobilization in adult female rats. Bone 14:153-159, 1993.

[94.] Matoba, H.; and Gollnick, P.D.: Response of skeletal muscle to training. Sports Med 1:240-251, 1984.

[95.] Merrilees, M.J.; and Flint, M.H.: Ultrastructural study of tension and pressure zones in a rabbit flexor tendon. Amer J Anat 157:87-106, 1980.

[96.] Michna, H.: Morphometric analysis of loading-induced changes in collagen-fibril populations in young tendons. Cell Tissue Res 236:465-470, 1984.

[97.] Mooney, V.; Nickel, V.; Harvey, J.P.; and Snelson, R.: Cast brace treatment for fractures of the distal part of the femur. J Bone Joint Surg 52-A:1563-1578, 1970.

[98.] Morgan, T.E.; Cobb, L.A.; Short, F.A.; Ross, R.; and Gunn, D.R.: Effects of long-term exercise on human muscle mitochondria. Adv Exp Med Biol 11:87-95, 1971.

99. Mosler, E.; Folkhard, W.; Knorzer, E.; Nemetschek-Gansler, H.; Nemetschek, T.H.; and Kock, M.H.J.: Stress-induced molecular rearrangement in tendon collagen. J Mol Biol 182:589-596, 1985.

100. Murray, P.D.F.: Bones: a study of the development and structure of the vertebrate skeleton. pp. 203. . Cambridge: Cambridge University Press. 1936.

101. Naveri, H.; Kuoppasalmi, K.; and Harkonen, M.: Metabolic and hormonal changes in moderate and intense long-term running exercises. Int J Sports Med 6(5):276-281, 1985.

102. Nilsson, B.E.; and Westlin, N.E.: Bone density in athletes. Clin Orthop 77:179-182, 1971.

103. Norton, L.A.; Rodan, G.A.; and Bourret, L.A.: Epiphyseal cartilage cAMP changes produced by electrical and mechanical perturbations. Clin Ortho Rel Res 124:59-68, 1977.

104. Noyes, F.R.; DeLucas, J.L.; and Torvik, P.J.: Biomechanics of anterior cruciate ligament failure: An analysis of strain-rate sensitivity and mechanisms of failure in primates. J Bone Joint Surg 56-A:236-253, 1974.

105. Noyes, F.R.; Torvik, P.J.; Hyde, W.B.; and DeLucas, J.L.: Biomechanics of ligament failure. II. An analysis of immobilization, exercise, and reconditioning effects in primates. J Bone Joint Surg 56-A:1406-1418, 1974.

106. O'Sullivan, M.E.; Bronk, J.T.; Chao, E.Y.S.; and Kelly, P.J.: Experimental study of the effect of weight bearing on fracture healing in the canine tibia. Clin Orthop 302:273-283, 1994.

107. Oettmeier, R.; Arokoski, J.; Roth, A.J.; Abendroth, K.; Jurvelin, J.; Tammi, M.; Kivranta, I.; and Helminen, H.J.: Subchondral bone and articular cartilage response to long distance running training (40 km per day) in the beagle knee joint. Eur J Exp Musculoskel Res 1:145-154, 1992.

108. Olah, E.H.; and Kostensky, K.S.: Effect of altered functional demand on the glycosaminoglycan content of the articular cartilage of dogs. Acta Biol Acad Sci Hung 23(2):195-200, 1972.

109. Palmoski, M.J.; and Brandt, K.D.: Aspirin aggravates the degeneration of canine joint cartilage caused by immobilization. Arth Rheum 25:1333-1342, 1982.

110. Palmoski, M.J.; and Brandt, K.D.: Effects of static and cyclic compressive loading on articular cartilage plugs in vitro. Arth Rheum 27(6):675-681, 1984.

111. Palmoski, M.J.; and Brandt, K.D.: Immobilization of the knee prevents osteoarthritis after anterior cruciate ligament resection. Arth Rheum 25:1201-1208, 1982.

112. Palmoski, M.J.; Colyer, R.A.; and Brandt, K.D.: Joint motion in the absence of normal loading does not maintain normal articular cartilage. Arth Rheum 23(3):325-334, 1980.

113. Palmoski, M.J.; Perricone, E.; and Brandt, K.D.: Development and reversal of a proteoglycan aggregation defect in normal canine knee cartilage after immobilization. Arth Rheum 22:508-517, 1979.

114. Parkkinen, J.J.; Lammi, M.J.; Helminen, H.J.; and Tammi, M.: Local stimulation of proteoglycan synthesis in articular cartilage explants by dynamic compression in vitro. J Orthop Res 10:610-620, 1992.

115. Piper, T.L.; and Whiteside, L.A.: Early mobilization after knee ligament repair in dogs: an experimental study. Clin Ortho Rel Res 150:277-282, 1980.

116. Purslow, P.P.: Strain-induced reorientation of an intramuscular connective tissue network: implications for passive muscle elasticity. J Biomech 22:21-31, 1989.

117. Retief, D.H.; and Dreyer, C.J.: Effects of neural damage on the repair of bony defects in the rat. Arch Oral Biol 12:1035-1039, 1967.

118. Roth, J.H.; Mendenhall, H.V.; and McPherson, G.K.: The effect of immobilization on goat knees following reconstruction of the anterior cruciate ligament. Clin Ortho Rel Res 229:278-282, 1988.

119. Roy, S.: Ultrastructure of articular cartilage in experimental immobilizations. Ann Rheum Dis 29:634-642, 1970.

120. Rubin, C.T.; Bain, S.D.; and McLeod, K.J.: Suppression of the osteogenic response in the aging skeleton. Calcif Tiss Int 50:306-313, 1992.

121. Saamanen, A.M.; Tammi, M.; Jurvelin, J.; Kiviranta, I.; and Helminen, H.J.: Proteoglycan alterations following immobilization and remobilization in the articular cartilage of young canine knee (stifle) joint. J Orthop Res 8:863-873, 1990.

122. Sah, R.L.-Y.; Kim, Y.-J.; Doong, J.-Y.H.; Grodzinsky, A.J.; Plaas, A.H.K.; and Sandy, J.D.: Biosynthetic response of cartilage explants to dynamic compression. J Ortho Res 7:619-636, 1989.

123. Salter, R.B.; Minster, R.R.; Bell, R.S.; and al., e.: Continuous passive motion and the repair of full-thickness articular cartilage defects: a one-year follow-up. Trans Orthop Res Soc 7:167, 1982.

124. Salter, R.B.; Simmonds, D.F.; Malcolm, B.W.; and al., e.: The biological effect of continuous passive motion on healing of full-thickness defects in articular cartilage: an experimental study in the rabbit. J Bone Joint Surg 62-A:1232-1251, 1980.

125. Sarmiento, A.: A Functional below-the-knee cast for tibial fractures. J Bone Joint Surg 49-A:855-875, 1967.

126. Sarmiento, A.; Schaeffer, J.F.; Beckerman, L.; Latta, L.L.; and Enis, J.E.: Fracture healing in rat femora as affected by functional weight-bearing. J Bone Joint Surg 59-A:369-, 1977.

127. Simkin, P.A.; Haung, A.; and Benedict, R.S.: Effects of exercise on blood flow to canine articular tissues. J Orthop Res 8(2):297-303, 1990.
128. Skerry, T.M.; Bitensky, L.; Chayen, J.; and Lanyon, L.E.: Loading-related reorientation of bone proteoglycan in vivo. Strain memory in bone tissue? J Orthop Res 6(4):547-551, 1988.
129. Slack, C.; Flint, M.H.; and Thompson, B.M.: The effect of tensional load on isolated embryonic chick tendons in organ culture. Conn Tissue Research 12:229-247, 1984.
130. Tammi, M.; Kiviranta, I.; Peltonen, L.; Jukka, J.; and Helminen, H.J.: Effects of joint loading on articular cartilage collagen metabolism: assay of procollagen prolyl 4-hydroxylase and galactosylhydroxylysyl glucosyltransferase. Conn Tiss Res 17:199-206, 1988.
131. Tammi, M.; Saamanen, A.-M.; Jauhiainen, A.; Malminen, O.; Kiviranta, I.; and Helminen, H.: Proteoglycan alterations in rabbit knee articular cartilage following physical exercise and immobilization. Conn Tiss Res 11:45-55, 1983.
132. Taylor, N.A.; and Wilkinson, J.G.: Exercise-induced skeletal muscle growth. Hypertrophy or hyperplasia. Sports Med 3(3):190-200, 1986.
133. Tesch, P.A.: Skeletal muscle adaptations consequent to long-term heavy resistance exercise. Med Sci Sports Exerc 20 Suppl 5:S132-134, 1988.
134. Thaxter, T.H.; Mann, R.A.; and Anderson, C.E.: Degeneration of immobilized knee joints in rats. J Bone Joint Surg 47-A:567-585, 1965.
135. Tipton, C.M.: Ligamentous strength measurements from hypophysectomized rats. Am J Physiol 221:1144-1150, 1971.
136. Tipton, C.M.; James, S.L.; Mergner, W.; and Tcheng, T.-K.: Influence of exercise on strength of medial collateral ligaments of dogs. Am J of Physiol 218:894-901, 1970.
137. Tipton, C.M.; Matthes, R.D.; Maynard, J.A.; and Carey, R.A.: The influence of physical activity on ligaments and tendons. Med Sci Sports 7(3):165-175, 1975.
138. Troyer, H.: The effect of short-term immobilization on the rabbit knee joint cartilage. Clin Ortho Rel Res 107:249-257, 1975.
139. Uhthoff, H.K.; and Jaworski, Z.F.G.: Bone loss in response to long-term immobilization. J Bone Joint Surg 60-B:420-429, 1978.
140. Vailas, A.C.; Tipton, C.M.; Matthes, R.D.; and Gart, M.: Physical activity and its influence on the repair process of medial collateral ligaments. Conn Tissue Res 9:25-31, 1981.
141. Viidik, A.: The effect of training on the tensile strength of isolated rabbit tendons. Scand J Plast Reconstr Surg 1:141-147, 1967.
142. Viidik, A.: The elasticity and tensile strength of the anterior cruciate ligament in rabbits as influenced by training. Acta Physiol Scand 74:372-380, 1968.
143. Viidik, A.: Tensile strength properties of Achilles tendon systems in trained and untrained rabbits. Acta Orthop Scand 40:261-272, 1969.
144. Vilart, R.; and Vidal, B.D.-C.: Anisotropic and biomechanical properties of tendons modified by exercise and denervation: Aggregation and macromolecular order in collagen bundles. Matrix 9:55-61, 1989.
145. Viru, A.: Plasma hormones and physical exercise. Int J Sports Med 13(3):201-209, 1992.
146. Vogel, K.G.; Keller, E.J.; Lenhoff, R.J.; Campbell, K.; and Koob, T.J.: Proteoglycan synthesis by fibroblast cultures initiated from regions of adult bovine tendon subjected to different mechanical forces. European J Cell Biol 41:102-112, 1986.
147. Vogel, K.G.; and Thonar, E.J.-M.: Keratan sulfate is a component of proteoglycans in the compressed region of adult bovine flexor tendon. J Ortho Res 6:434-442, 1988.
148. Walsh, S.; Frank, C.; and Hart, D.: Immobilization alters cell metabolism in an immature ligament. Clin Orthop 277:277-288, 1988.
149. Wang, C.W.; Weiss, J.A.; Albright, J.; Buckwalter, J.A.; Martin, R.; and Woo, S.L.-Y.: Life-long exercise and aging effects on the canine medial collateral ligament. Tran 36th Ann Meeting Ortho Res Soc 1990.
150. Williams, J.M.; and Brandt, K.D.: Immobilization ameliorates chemically induced articular cartilage damage. Arth Rheum 27:208-216, 1984.
151. Williams, J.M.; Moran, M.; Thonar, E.J.; and Salter, R.B.: Continuous passive motion stimulates repair of rabbit knee articular cartilage after matrix proteoglycan loss. Clin Orthop 304:252-262, 1994.
152. Woo, S.; Maynard, J.; Butler, D.; Lyon, R.; Torzilli, P.; Akeson, W.; Cooper, R.; and Oakes, B.: Ligament, tendon, and joint capsule insertions into bone. in Woo, S.L.-Y.; and Buckwalter, J.A., Editors: Injury and Repair of the Musculoskeletal Soft Tissues, pp. 129-166. Park Ridge, IL: American Academy of Orthopaedic Surgeons, 1988.
153. Woo, S.L.; Gomez, M.A.; Amiel, D.; et al.: The effects of exercise on the biomechanical and biochemical properties of swine digital flexor tendons. J Biomech Eng 103:51-56, 1981.
154. Woo, S.L.-Y.; Gomez, M.A.; Sites, T.J.; Newton, P.O.; Orlando, C.A.; and Akeson, W.H.: The biomechanical and morphological changes in the medial collateral ligament of the rabbit after immobilization and remobilization. J Bone Joint Surg 69-A:1200-1211, 1987.
155. Woo, S.L.-Y.; Horibe, S.; Ohland, K.J.; and Amiel, D.: The response of ligaments to injury: healing of the collateral ligaments. in Daniel, D.;Akeson, W.H.; and

O'Connor, J.J., Editors: Knee Ligaments: Structure, Function, Injury, and Repair, pp. 351-364. New York: Raven Press, 1990.

156. Woo, S.L.-Y.; Matthews, J.V.; Akeson, W.H.; Amiel, D.; and Convery, F.R.: Connective tissue response to immobility. Arth Rheum 18:257-264, 1975.

157. Woo, S.L.-Y.; Ritter, M.A.; Amiel, D.; Sanders, T.M.; Gomez, M.A.; Kuei, S.C.; Garfin, S.R.; and Akeson, W.H.: The biomechanical and biochemical properties of swine tendons - long term effects of exercise on the digital extensors. Conn Tiss Res 7:177-183, 1980.

158. Woo, S.L.-Y.; and Tkach, L.V.: The cellular and matrix response of ligaments and tendons to mechanical injury. in Leadbetter, W.B.; Buckwalter, J.A.; and Gordon, S.L., Editors: Sports Induced Inflammation - Basic Science and Clinical Concepts, Park Ridge IL: American Academy of Orthopaedic Surgeons, 1990.

159. Woo, S.L.-Y.; Wang, C.W.; Newton, P.O.; and Lyon, R.M.: The response of ligaments to stress deprivation and stress enhancement: biomechanical studies. in Daniel, D.;Akeson, W.H.; and O'Connor, J.J., Editors: Knee Ligaments: Structure, Function, Injury, and Repair, pp. 337-350. New York: Raven Press, 1990.

160. Yamamoto, N.; Ohno, K.; Hayashi, K.; Kuriyama, H.; Yasuda, K.; and Kaneda, K.: Effects of stress shielding on the mechanical properties of rabbit patellar tendon. J Biomech Eng 115:23-28, 1993.

161. Yeh, C.-K.; and Rodan, G.A.: Tensile forces enhance prostaglandin E synthesis in osteoblastic cells grown on collagen ribbons. Calcif Tissue Int 36:S67-S71, 1984.

162. Zuckerman, J.; and Stull, G.A.: Effects of exercise on knee ligament separation force in rats. J Appl Physiol 26(6):716-719, 1969.

163. Zuckerman, J.; and Stull, G.A.: Ligamentous separation force in rats as influenced by training, detraining, and cage restriction. Med Sci Sports 5(1):44-49, 1973.