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Chapter 7
The Structure and Function of Joints

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Few examples in nature support the tenant that “form follows function” as closely as the human synovial joint. Evolution has provided humans with superb limb articulation that supports an almost unique ability to move while upright and has an exquisite mixture of efficient force transfer, low friction surfaces, and shock absorption capacity. In this chapter the biochemical, cellular, and biomechanical aspects of joints are discussed and the critical areas of joint physiology important to the performance of the normal joint and the development of the arthritides are addressed. Although all joints are considered, synovial joints and the intervertebral articulations are emphasized because they constitute most joints and are most often involved by the disease processes discussed in this volume.

CLASSIFICATION OF JOINTS

Joints are most often classified according to the type of motion they allow. Three types are recognized: immovable joints (synarthroses), slightly movable joints (amphiarthroses), and movable joints (diarthroses) (1). They can also be classified by the nature of the specialized forms of connective tissue present (1). The two classifications are interrelated because the architecture and tissue construction of the joints determines their relative mobility. Fibrous or cartilaginous membranes (syndesmoses or synchondroses) connect the bony ends of the immovable or slightly movable joints. In contrast, the component bony parts of the movable joints, although covered by hyaline cartilage, are completely enclosed by a joint cavity lined by a synovial membrane (synovial or diarthrodial joints) (1,2).

Synarthroses (nonmovable joints) are generally found in the skull. Here, the bony plate ends that comprise the joints are held together by fibrous or cartilaginous elements. Amphiarthroses are characterized by the presence of broad, flattened discs of fibrocartilage connecting the articulating surfaces. The bony portions of the joint are usually covered by hyaline cartilage, and a fibrous capsule invests the entire structure. Such joints are those between the vertebrae, the distal tibiofibular articulation, the pubic symphysis, and the upper two thirds of the sacroiliac joint. Diarthroses include most of the joints of the extremities. The joint spaces—broad expanses of smooth articular cartilage and loosely

applied synovial membranes—allow the wide ranges of motion necessary for locomotion and grasp (1,2).

SYNOVIAL JOINTS

General Structure

Synovial (diarthrodial) joints account for most of the body's articulations and are characterized by wide ranges of almost frictionless movement. The articulating bony surfaces are usually bulbous, sometimes flattened excrescences of cancellous bone, capped by a thin plate of dense cortical bone (the subchondral plate), which is covered by articular cartilage. There is an intermediate layer of calcified cartilage between the subchondral plate and the articular cartilage. Beneath the bony end plate, making up the bulk of the articulating end, lies cancellous bone. In adults, this may contain fatty marrow, whereas in children, it represents the distalmost portion of the epiphysis (growth center) and, thus, frequently contains red (hematopoietic) marrow. The articular cartilage is adherent to the bony end plate and bound by a set of collagen fibers, which run from the articular cartilage into intervening calcified cartilage, and perhaps even into the bone. This hyaline articular cartilage is a specialized form of smooth and resilient connective tissue that serves as the bearing and gliding surface. The joint cavity is a tissue space containing a thin layer of synovial fluid (see Chapters 4 and 8) (Fig. 7.1).

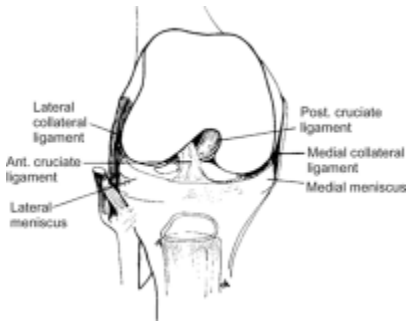

FIG. 7.1. Human knee joint. The patella and capsule have been removed. Note that the distal femur and proximal tibia are covered by hyaline articular cartilage. Affixed to the surface of the tibia are the medial and lateral menisci. The medial and lateral collateral ligaments and stout collagenous bands provide stability in the coronal plane. The cruciate ligaments control stability in the sagittal plane.

The movement of the cartilaginous surfaces on one another provides the joint with the almost frictionless mobility essential to function. However, to function effectively, joints must be stabilized within their sockets to prevent slipping out of place, with concomitant loss of control. Stability within the joint's bony configuration is primarily the function of the muscles surrounding the joint. (3). The ligaments and capsule mainly act to guide the joint and can act to limit the extent of the motion. However, failure of appropriate concerted and timely muscle action can place the ligaments and capsules under excessive strain, and they can be torn (3). Each joint has a unique configuration that dictates its range of motion. For example, the hip is a ball and socket; the knee is a rounded, condylar, cam-shaped, four-bar linkage that allows flexion and extension, coupled with a small amount of rotation; the ankle is a complexly shaped mortised hinge; and the shoulder is a ball on a disc. The intervertebral segmental articulations are a combination of an amphiarthrosis (bony end plates connected by a fibrocartilaginous disc) and two diarthrodial joints (the intervertebral

facet joints), which allow considerable motion but provide great stability.

The configuration of each individual joint provides an appropriate contact area for the usual positions of loading. This anatomy, combined with appropriate leveraged muscle action, allows for high-efficiency performance (4). The joint contact areas provide for intraarticular stress levels within the tolerance of the tissues involved (~1,000–2,000 kPA or 150–300 psi) (5). Joint design expresses the trade-off between stability and range of motion. The ankle joints need great stability to provide a platform for a standing or moving body, but for efficient gait, they must also flex and extend. This is accomplished with considerable bony stability, and the distal leg bones create a stirrup or mortise encompassing the talus, essentially forming a hinge joint. The medial malleolus, anterior lip, and posterior margin of the tibia and the fibular malleolus prevent abnormal movement by bony impingement on the talus and provide the stability necessary for normal dorsi and plantar flexion under heavy loads. On the other hand, the shoulder is at the base of the carrying and throwing extremity and, to be effective, needs a wide range of motion. This is accomplished with a shallow, nonrestraining, ball and shallow socket bony configuration, which contributes little to shoulder stability. It is concerted muscle action that provides shoulder stability (6).

Accessory structures that aid in maintaining the integrity of the joint are the fibrous capsule and ligaments (7,8). The fibrous capsule, for most joints, is a firm structure consisting of dense connective tissue that invests the entire joint and usually inserts into the bones close to the articulating surfaces. Within the capsule are thick bands or condensations of parallel collagen fibers known as ligaments. These, too, insert on the bony parts and vary in their tightness between anatomic sites, depending considerably on the position in which the joint is placed.

Within the joint capsule, and defining the intraarticular space is a specialized layer of connective tissue cells, the synoviocytes, that secrete the synovial fluid (9,10). Deep to this layer are varying amounts of highly vascular adipose, fibrous, or areolar tissue supporting the synoviocytes. This

allows the sac to be appropriately loose to allow the joint a range of motion without limitation and to keep the synovial folds from becoming entrapped between the joint surfaces (11,12). The synovial sac faithfully replicates the inner surface of the capsule, is reflected at the capsular insertion into the bone, and then extends along the bone to the margin of the articular cartilage (11). The synovial tissue is endowed with a rich blood supply necessary not only to support the synoviocytes, but also to serve as the source of the synovial fluid. The capsule has numerous nerve endings (10) that, along with the spindles in the muscles, ligaments, and tendons, are responsible for keen proprioceptive sense, deep pain perception, and sensation of distention. These afferent stimuli protect the joints and give us a sense of where they are in space (13,14,15).

Certain joints have within their cavities complete or, more often, incomplete fibrocartilaginous discoid structures known as menisci. The menisci are rudimentary in some areas (e.g., acromioclavicular joint) and highly developed and well defined in others (e.g., knee, temporomandibular joint, and sternoclavicular joints) (1). Synovium does not cover fibrocartilaginous menisci, which are firmly fixed to the joint margin by attachment to bone and to ligaments or capsule, preventing abnormal movement or intraarticular

displacement during joint function. As with articular cartilage, menisci are essentially aneural. The function of the menisci varies from site to site, but most authorities feel they primarily contribute to joint stability, shock absorption, and proper tracking of the bony ends during motion. They exist in hinge joints where some rotation is required (16).

Embryology and Development

Recent studies have elucidated the molecular interactions that contribute to the embryonic development of synovial joints. Joint development is considered to take place in three major phases following the appearance of primordial long bones from condensations of mesenchymal tissue. These early bone buds are composed of cartilage precursor cells that eventually branch. Joints first appear at 6 weeks of gestation, when areas of high cell density (interzones) appear. The initial joint demarcation is characterized by a homogeneous interzone created between the chondrifying skeletal elements of the long bones. Next, a three-layered interzone develops that is composed of two chondrogenic layers separated by an intermediate layer.

Cells begin to differentiate away from the prechondrogenic morphology at this stage and mature into densely packed cells with a flattened appearance. This is accompanied by a reduction in the gene expression of type II collagen and other cartilage specific genes. The external mesenchymal tissue forms the joint capsule and tendons, whereas the internal mesenchymal layer forms the synovial membrane and meniscus, typically at 7 weeks. Finally (at around 8 weeks) cavitation occurs to create the articular cavity. Although the initiation of cavitation is independent of articular motion, the final differentiation of the synovial space appears to depend on movement (17,18).

Immobilization of the developing joint through the use of neuromuscular blocking agents resulted in decreased hyaluronan (HA) synthesis and the surface expression of its receptor, CD44, and ultimately, failure of the cavitation process. The expression of HA is central to cavitation, probably through the disruption of cohesion between interzone cells (19), which may trigger apoptosis (programmed cell death) that takes place mainly in the central interzone and partly in the most internal regions of the synovial mesenchymal tissue (20). However, recent studies suggest that the role of apoptosis in cavitations may be restricted to a later time point and only involve hypertrophic chondrocytes in the epiphyseal cartilage and at the growth plate (21).

Although the precise factors that dictate this developmental process remain to be elucidated, a number of key cell signals have been identified that have important regulatory effects. *Wnt14*, a member of the *Wnt* family of cell signaling molecules, appears to exert a critical influence. *Wnt* genes encode locally-acting growth factors, which function to signal cells adjacent to the site of Wnt protein production. Most of the components of the *Wnt* signaling pathway exert an effect on levels and activity of β-catenin, which forms a complex with cadherin that is essential for cell adhesion. The pattern of *Wint14* expression in the embryonic joint suggests that this signaling molecule regulates the segmentation of the mesenchymal condensations (22). High *Wint14* levels appear as prechondrogenic cells differentiate into interzone tissue cells, and this *Wnt14* gene activity is sustained throughout the life of the synovial membrane. The Wnt14 protein regulates downstream gene activity involving *Gdf5* (growth differentiation factor 5, which is also known as

cartilage-derived morphogenetic protein 1), autotaxin (an autocrine motility factor), and chordin (an inhibitor of bone morphogenetic proteins), which subsequently block critical differential events in nearby prechondrogenic cells. Thus, the diffusion area of Win14 protein regulates the appearance of the different interzones and may be essential for the correct spacing of the joints. Spitz and Duboule (23) have proposed an attractive hypothesis in which the appearance of the initial joint in an embryonic limb determines the position of the next joint (and so on) via *Win14* expression, although the regulation of the development of the first interzone remains to be explained. However, there are several candidate gene activities for the initial differentiation, including *Cux1* (a homologue of the *Drosophila Cut* gene), which encodes a large transcriptional factor with a single homeodomain and multiple DNA-binding motifs. *Cux1* has been implicated in the formation of the apical ectodermal ridge, which controls the development of the vertebrate limb bud (24) and is precisely expressed in regions of incipient joint formation. *Cux1* activity appears at the time of prechondrogenic cell differentiation into interzone cell tissue, and this gene has

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been demonstrated to regulate the conversion of chondrocytes into the nonchondrogenic cells characteristic of the interzone (25). In addition, the expression of the *Hox* family genes within the developing limb is critical to the positioning of the joints. The function of this gene family is usually exerted through cell patterning, but there is evidence that *Hox* genes may directly regulate chondrogenesis via changes in chondocyte proliferation or cell adhesion (26).

As the joints develop, the role of bone morphogenetic proteins (BMPs) and their GDF subclass become central. BMPs are part of the transforming growth factor-b superfamily, noted for their ability to induce endochondral bone formation and fracture healing. In the developing embryo, BMPs also control aspects of joint development (27), possibly through their capacity to regulate apoptosis, cell proliferation, and connective tissue matrix production (28). In most situations, BMPs may work together with GDFs, but there is evidence to suggest that the interaction of BMP and GDF-5 varies among different joints. Since these factors may act on the same receptor, differences in the levels of expression may be critical to joint development. Different concentrations and varied complex formations (either homodimers or heterodimers) between these factors may influence whether BMP/GDF production results in proliferation, differentiation, or apoptosis. For instance, the capacity of BMP-7 to promote alkaline phosphatase activity is significantly reduced by the coexpression of GDF-5 (29). BMP and GDF signaling may be modulated at the protein level through interactions with chordin, follistatin, or noggin (all of which antagonize receptor binding) or at the gene regulatory level through the *Smad1* pathway. Noggin appears during early cartilage condensation, becoming restricted to the epiphyseal cartilage (30), whereas chordin expression remains sustained through joint development. These antagonists may control joint formation by preventing the local promotion of chondrogenesis by BMPs and effect regulation simply by differential diffusion rates (between the agonists and antagonists) in the tissue (19). Fibroblast growth factors (FGFs) also regulate BMP activity and may inhibit chondrocyte differentiation and proliferation (31). FGF cell signaling is mediated through the Erk family of MAP kinases and may control phosphorylation of *Smad1*. Mutations in the FGF3 receptor that result in enhanced

activation are well recognized to result in the shortened proximal limb bones characteristic of achondroplasia. FGFs are expressed during the early stages of limb formation (32), may inhibit the induction of chondrogenesis by BMPs, and affect chondrogenic pattern formation, resulting in the formation of a cartilaginous mass surrounded by a set of regularly spaced nodules (33). It has been suggested that differential expression of FGF receptors within the developing joint may determine the cell signaling function, with FGF-R1 mediating mesenchymal mitogenesis, FGF-R2 serving as an inhibitory signal, and FGF-R3 up-regulating cartilage mitogenesis.

As true cartilage tissue appears, chondroblasts rapidly secrete extracellular matrix and establish the growth plates. Their proliferation acquires unidirectional characteristics, resulting in the hallmark columnar appearance. This differentiation appears to be controlled via *Sox* genes, with *Sox9* expressed from the prechondrytic to the prehypertrophic stage, which serves as an activation factor for cartilage specific genes such as *Col2a1. Sox5* and *Sox6* are coexpressed, and may serve as cofactors in the production of type II collagen and aggrecan (34). Furthermore, the transcriptional factor scleraxis may interact and diverge with *Sox9* activity to determine the development of the tendons (35). The development of a bone with articulations at its ends occurs from a cartilaginous anlage at various times for various bones. At birth, the only secondary center of ossification that is radiographically apparent is at the proximal end of the tibia. The rest begin to appear about the third or fourth month of life. A vessel grows into the center of each cartilaginous long bone precursor and forms a marrow cavity, the primary center of ossification. The proximal and distal ends of this cavity form the growth plates (epiphyseal plates) and are responsible for the bone's longitudinal growth, whereas the remaining cartilaginous ends of the bones are invaded in a similar manner by a vessel, which form the secondary centers of ossification responsible for the growth of the articular ends.

STRUCTURE AND COMPONENTS OF THE JOINT'S CONSTITUENT PARTS

Articular Cartilage

The articular cartilages (Fig. 7.2) are the principal surfaces of the diarthrodial joint, and they, and the synovial fluid, are responsible for the almost frictionless movement of the articulating surfaces on each other (36). These specialized connective tissues measure less than 5 mm in thickness in human joints (37), with considerable variation depending on the joint and location within the joint (38,39). Articular cartilage is dense white on gross inspection, tending to become somewhat yellow with age (40). Despite the high water content, cartilage feels semirigid. Contrary to expectations, the surface is not smooth, and a number of studies using the scanning electron microscope have demonstrated gentle undulations and irregular depressions that appear to correspond to the location and shape of cells lying just beneath the surface (37,41,42). These depressions average 20 to 40 μm in diameter and occur with an approximate frequency of 430/mm^2 (43,44) (Fig. 7.3). The irregularities of the surface, evident on scanning electron microscopic studies, may be important in providing a site for attachment of a fine filamentous gliding protein, also known as lubricating glycoprotein (45).

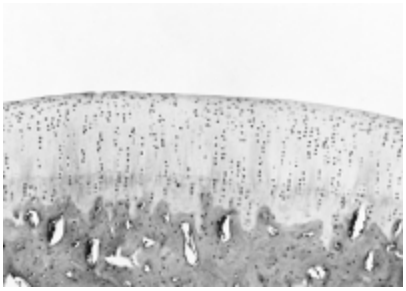

FIG. 7.2. Low-power photomicrograph of adult articular cartilage. Note the zonal distribution of the cells, the calcified layer separated from the radial zone by the tidemark, and the cortical bone of the underlying bony end plate. Articular cartilage is sparsely cellular, and the bulk of the tissue consists of extracellular matrix (hematoxylin and eosin, original magnification × 40).

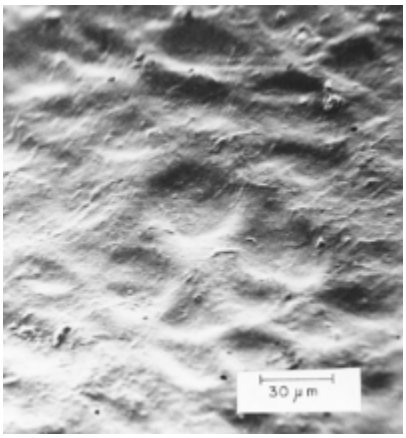

FIG. 7.3. Scanning electron micrograph of the surface of articular cartilage demonstrating irregularly placed rounded or ovoid depressions averaging 20 to 40 µm in diameter (original magnification × 440). (Courtesy of Dr. Ian Clark.)

In adults, articular cartilage is aneural, avascular, and alymphatic. The subchondral plate in healthy humans is

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impervious to blood vessels. Articular cartilage derives its nutrition by a double diffusion system (11,37,46). Because the blood vessels in synovium are situated along the capsular (outer) surface (47), nutrients must first diffuse across the synovial membrane into the synovial fluid and then through the dense matrix of the cartilage to reach the cartilage cells, the chondrocytes (48,49). These are, for the most part, embedded in the cartilage matrix (11,48,49). The diffusion of materials is not simple, in that molecular size, charge, and configuration all play a role in the traverse across the matrix to reach the cell (37). Because there are no nerves in articular cartilage, vertebrates must depend on nerve endings in the capsule, muscles, and subchondral bone for appreciation of pain and proprioception (13,14,15,50,51). Although articular cartilage exists as a critical part of the joint organ, as in any organ, full function depends on the entire tissue composition.

Histologic and ultrastructural examination of the cartilage demonstrates a preponderance of extracellular matrix and only sparse cellularity (46,52) (Fig. 7.4). The distribution of cells is not random. Three more or less distinct zones have been described (37,53): a tangential or

gliding zone, in which elongated fibroblast-like cells lie with their long axes parallel to the surface; a transitional zone, in which the cells are rounded and appear randomly distributed; and a radial zone, in which the cells appear to line up in short, irregular columns. The cells of cartilage are sparse in number and, in adults, are widely separated from one another. There are no bridges, cell-cell interactive systems, or processes that abut, as are commonly seen in other tissues. The asymmetric organization of cells and tissue architecture from the surface to deep layers of articular cartilage reflects the nonuniform distribution of its major macromolecular components, namely collagen and proteoglycans. Biochemical details of these molecules are addressed in Chapters 9,10, and 11.

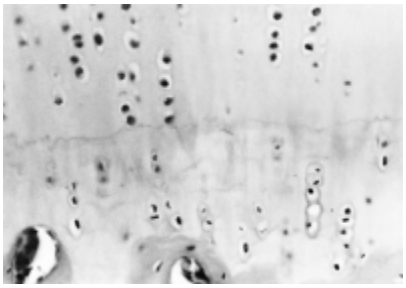

FIG. 7.4. Photomicrograph of mature articular cartilage showing the tidemark, a wavy bluish line (or series of lines) separating the calcified zone below from the radial zone above. The matrix and cells of the calcified zone are heavily encrusted with apatitic salts (hematoxylin and eosin, original magnification × 250).

The water content in articular cartilage can be almost 80% (53). Most of the water is freely exchangeable with synovial fluid solute and, except for a small component of “bound water” (37), appears to be held in the form of proteoglycan collagen gel (53). The movement of water and,

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more specifically, “weeping” of the cartilage may be essential features of a boundary lubrication system (54,55). Such weeping from the cartilaginous surface, under compression, can cause articular cartilage to temporarily lose up to 20% of its height. When the pressure is removed, water from the joint fluid is imbibed, and the cartilage swells back to its original height (56).

Collagen is the most prevalent organic constituent in articular cartilage, accounting for over 50% of the remaining material (46). The most superficial collagen fibers are arranged in bundles and sheets parallel to the surface of the cartilage, forming a “skin.” Vertical fibers extend upward from the subchondral bone (57). These lowermost fibers are perpendicular to the surface and firmly fixed to the underlying bone, thus resisting shear (Fig. 7.5). Collagen in the middle layer appears to be randomly orientated (Fig. 7.6). This appearance belies the overall arcadelike orientation of the articular cartilage collagen, hooplike from the base and arching to just below the surface. These were first described by Benninghoff in 1925 (58,59). The problem with this observation is that collagen fibers are not that long. Electron microscopy finally clarified the situation. The Benninghoff hoops are made up of

the basal vertical collagen, the surface horizontal collagen, and the midzone collagen, which is arranged in a more vertical than horizontal way (60). When compressed, however, the midzone collagen lies more horizontal than vertical, the better to resist compressive load (61) (Fig. 7.6). It is a clever engineering construct.

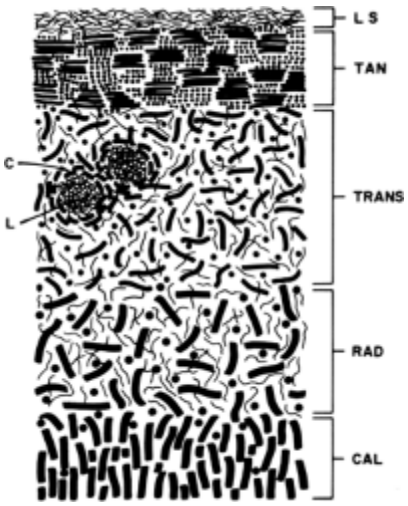

FIG. 7.5. The fibrous architecture of human articular cartilage according to a scheme proposed by Lane and Weiss. The lamina splendens (*LS*) is a layer several microns deep, composed of the fine fibers that cover the articular surface. Beneath this lies the tangential zone (*TAN*), which consists of tightly packed bundles of individual collagen fibers arranged parallel to the articular surface, often at right angles to each other. The collagen fibers in the transitional zone (*TRANS*) are randomly arranged. Collagen fibers of the radial zone (*RAD*) are also randomly arranged, but are of larger diameter, whereas those of the calcified zone (*CAL*) are arranged perpendicular to the articular surface. (From Lane JM, Weiss C. Current comment: review of articular cartilage collagen research. *Arthritis Rheum* 1975;18: 558, with permission.)

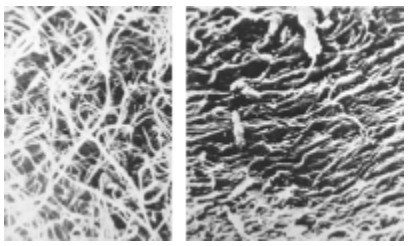

FIG. 7.6. Left: A scanning electron micrograph of the midzone collagen fibers of articular cartilage in the unloaded state. Note the essentially random orientation. **Right:** The same area of the cartilage with compressive load applied. Note how the fibers line up perpendicular to the load. (From McCall J. Load deformation response of the microstructure of articular cartilage. In: Wright V, ed. *Lubrication and wear in joints*. London: Sector, 1969:39–48, with permission.)

The fibrous collagenous network exhibits mechanical connectivity throughout the tissues. The major component of this network is type II collagen. The fibrils formed are highly cross-linked via the amino groups on lysine residues. Numerous other collagen types are present and serve to modify the nature of the fibril and may provide additional cross-linking of collagen molecules. In addition, matrix macromolecules are present that also interact with collagen, some adding additional cross-links. The spacing and organization of collagen fibrils entrap the proteoglycan aggrecan, preventing its diffusion within and out of the tissue. Aggrecan is over 2 million daltons in molecular weight. Nearly 80% of its mass consists of chondroitin sulfate glycosaminoglycan chains. These chains are polymers of sugars that are negatively charged. Each chain contains about 100 sugars, each sugar containing a negative charge. There

are about 100 chains per aggrecan. Each molecule, then, has a charge of about -10,000. These molecules are found in cartilage at concentrations between 50 and 100 mg/mL. Such a concentration of charges results in considerable electrostatic interactions between the fixed proteoglycans and mobile counterions. It is the electrostatic forces between adjacent glycosaminoglycan chains that account for much of the swelling pressure in cartilage (62).

The chemistry of normal articular cartilage varies within each joint and from joint to joint (63). Higher concentrations of proteoglycan and collagen molecules are found in habitually load-bearing areas and are associated with greater interarticular pressures. It is the hydrostatic pressure within the articular cartilage that controls cellular production of cartilage extracellular matrix. Chondrocyte cytoskeletons apparently sense deformation and induce the metabolic changes that determine the tissue's extracellular chemical composition (64). Pauwels, from his analysis of fracture malunions, suggested that cartilage forms from mesenchymal stem cells under hydrostatic pressure, which is the condition in the confined compression of articular cartilage (65,66,67). This has been verified experimentally (68).

Calcified Cartilage

A layer of calcified cartilage exists in the interface between the articular cartilage and its underlying (subchondral) bone. The articular cartilage and its calcified cartilage bed are separated from the bone by a wavy, irregular bluish line (on hematoxylin and eosin staining) called the tidemark (69,70) (Fig. 7.4). The tidemark is similar in appearance and composition to the cement lines in bone and may act as a limit to calcification (71,72). The collagen in calcified cartilage is type II and it is heavily encrusted with hydroxyapatite. This tissue contains cells that are metabolically active (73). The deep surface of the calcified cartilage merges with the endplate of the underlying bone (70) (Fig. 7.4) in an undulating interface. Redler and co-workers (70) have suggested that this permits a significant increase in resistance to shearing forces and helps to keep the cartilage on its bony bed. The fibers in the lowermost region are perpendicular to the surface and firmly fixed to the underlying calcified subchondral structures, also positioned to resist shear (Fig. 7.5).

Abnormal joint pressures cause remodeling of calcified cartilage, which was once thought to be effite but has more recently been shown to be quite dynamic (74). This tissue appears to heal microdamage by vascular ingrowth (73). In pathologic situations, such as osteoarthrosis, vessels penetrate the subchondral plate and the calcified cartilage (52,75). The calcified cartilage can then act as a source of enchondral calcification, remodeling the subchondral plate and creating a new tidemark (71). After substantial remodeling, as in osteoarthrosis, the tidemark may be duplicated or even appear as multiple lines (76).

Subchondral Bone

Although, at the tissue level, the bone located in the subchondral plate and the cancellous bone that supports it are indistinguishable from bone in other sites, the organization of the subchondral bone is specific. The subchondral plate on which the calcified cartilage lies is thinner than cortical bone in most sites and contains variable numbers of mature haversian systems. These systems run parallel to the joint rather than parallel to the long axis of the

bone (Fig. 7.7). The sheets and interconnecting struts of cancellous bone, which support the plate and fill the epiphyseal end of the bone, differ considerably from joint to joint, but are highly ordered and characteristic for any one joint. The major plates are arranged at right angles to the predominating stresses and, together with the subchondral bony plate, are approximately 10 times more deformable than is the cortical bony shaft (77). An increase in this bony structure, so-called subchondral sclerosis, is associated with thickening of the subchondral plate, advance of the tidemark, and thinning of the overlying articular cartilage. These changes are pathognomonic of osteoarthrosis and are deleterious to the function of the joint and the health of the overlying articular cartilage (78,79).

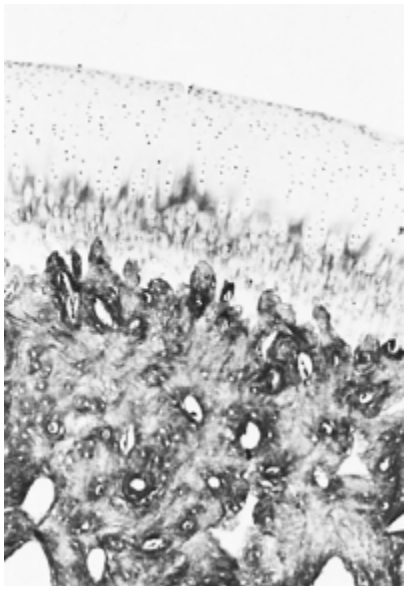

FIG. 7.7. Photomicrograph of distal femur of an adult rabbit showing the subchondral bone. Note the relationship of the bone to the cartilage and the compact nature of the subchondral plate. The Haversian canals appear to be parallel to the joint surface (Masson trichrome, original magnification × 50).

Synovial Membrane

The synovial membrane serves two functions in the adult joint: the provision of nutrients to cells of the articular cartilage and the production of lubricating fluid to ensure the

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low friction characteristic of joint articulation. The membrane consists of two distinct layers: the thin intimal lining or synovial surface layer, and the subintimal layer of connective tissue that supports both the lining and the blood vessels that supply the membrane. The synovial lining produces synovial fluid and represents the direct interface to the intraarticular cavity. In the normal condition, it is an irregular membrane merely two to three cells thick (Fig. 7.8). In inflammatory disease, this appearance can change dramatically, with both hypertrophy and hyperplasia rapidly developing, resulting in an inflammatory, fibrous membrane. The main cells of the synovial surface layer and its vascular sublining have been historically divided into two distinctive populations, historically termed synovial type A cells and synovial type B cells. Type A cells have a macrophage morphology, whereas type B cells appear fibroblastic. This terminology has fallen from use with the recent recognition that synovial type A cells are actually bone marrow-derived macrophages, which integrate with the resident fibroblast population that

comprises the majority of the cells in the synovium. Ultrastructure studies have shown that there is no basement membrane beneath the synovial intima (79), although both laminin and type IV collagen may be found underlying the synovial intima. Subintimal tissue is sparsely populated with cells compared with the intima, and fat cells and blood vessels are integrated within this matrix, which is rich in type I and type III collagen, proteoglycans, and fibronectin (80).

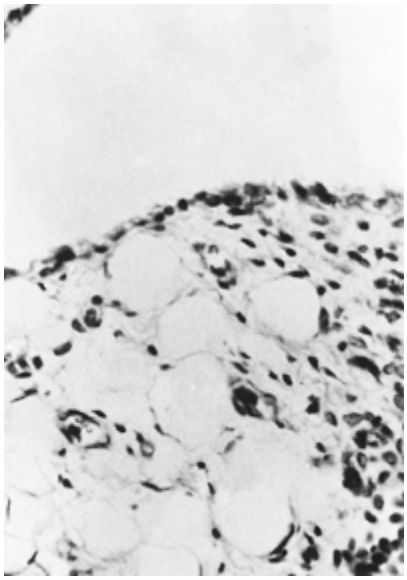

FIG. 7.8. Photomicrograph of normal synovium showing the surface layers of synovial cells and the presence of areolar and fatty synovial tissue (hematoxylin and eosin, original magnification × 225).

Cell Biology of the Synovial Membrane

The cell biology of the synovial lining cells of the intima and the deeper subintimal cells reflect many of the functions ascribed to the distinct layers. Cellular activities and protein production can be examined in great detail using immunohistochemistry, and both the intracellular proteins and cell differentiation markers provide insights into the functions and interactions of the cells that comprise the synovial membrane. Intimal macrophages stain positive for nonspecific esterase, and they can be distinguished by a variety of cell surface markers that vary between the cells resident in the intima and those within the subintima. Synovial macrophages express high levels of CD68, a 110-kd type I transmembrane glycoprotein localized in the cytoplasmic granules of monocytes and macrophages. CD68 is also found in granulocytes, dendritic cells, myeloid progenitor cells, and hematopoietic bone marrow progenitor cells. It is a member of the sialomucin family, and its function has not been fully elucidated. High CD68 expression is relatively consistent on macrophages throughout the synovial tissue, and class II major histocompatibility complex DR antigen expression is also invariant on macrophages throughout the normal joint (81,82). CD14, which is expressed at a higher level on subintimal cells than intimal macrophages, is a glycosylphosphatidylinositol membrane protein, found on neutrophils and B lymphocytes in addition to macrophage/ monocyte lineage cells. CD14 is part of the heteromeric lipopolysaccharide (LPS) receptor complex that also contains Toll-like receptor 4 (TLR4), responsible for early innate immune recognition of microorganisms (83). CD14 binds LPS

and associates with TLR4, resulting in the transduction of an activation signal (84).

Both synovial lining macrophages and subintimal cells express markers of the lymphocyte function-associated family, which mediate intercellular and cell matrix adhesion interactions. These molecules consist of a common β chain (95 kd) associated with different α chains to produce CD11a, CD11b, or CD11c. Intimal macrophages are essentially restricted to the expression of CD11b, which binds to the complement component iC3b, extracellular matrix proteins, and the third extracellular domain of CD54 intercellular adhesion molecule-1 (ICAM-1). Subintimal macrophages also express CD11a, which mediates a wider variety of leukocyte functions, including interactions with endothelial cells (81).

Synovial macrophages also express all three variants of the receptors for the Fc portion of the immunoglobulin molecule (FcR). However, the ratio of FcγRIII (CD16) to FcγRI (CD64) appears high on intimal macrophages and low on subintimal cells. Fc receptors mediate reactions between cells, antibodies, and immune complexes, and the

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class of the FcR can determine whether binding leads to an activation signal resulting in phagocytosis, degranulation, or superoxide production, or to an inhibitory signal. Furthermore, the affinity for the different immunoglobulin G subclasses is influenced by polymorphisms within the FcγRIIa, FcγRIIIa, and FcγRIIIb genes (85). It has been observed that the expression of cell surface markers varies between macrophages resident in the intima and the subintimal lining layers. The differences in surface antigen expression may reflect functional differences between the populations, or a maturation of acquired markers as the cells traffic from the circulatory system to the surface of the synovial lining, although the precise significance of the variation remains unknown. Interestingly, synovial macrophages are remarkable for the absence or low expression of markers typically seen on tissue macrophages, notably CD15a (a carbohydrate component of adhesion molecules), CD25 [interleukin-2 (IL-2) receptor], CD34 (a progenitor cell marker), and CD35 (which binds the complement components C3b and C4b) (81).

Cell markers expressed by the synovial fibroblasts allow a clear distinction between the two population of synovial cells using immunohistochemical techniques (Table 7.1). Intimal fibroblasts are characterized by high uridine diphosphoglucose dehydrogenase (UDPGD) activity. This enzyme catalyzes glycosaminoglycan formation, and its expression within the synovial fibroblast appears related to the high level of UDP-glucuronate production, which forms HA by copolymerization with UDP-*N*-acetylglucosamine (86). Synovial fibroblasts also express high levels of CD55, or complement decay accelerating factor (DAF) (87). DAF is an approximately 70–kd transmembrane glycoprotein with a glycosylphosphatidylinositol tail that binds to activated C4b or C3b complement fragments on cell surfaces, and is also a coligand for the G protein-coupled activation antigen CD97. Its action on complement components both prevents the assembly and accelerates the degradation of complement acting in either classical or alternative pathways. The expression of fibroblast DAF may be related to the macrophage expression of FcRγRIIIa and could determine the response to immune complexes that form within the synovial tissue during infection or autoimmune connective tissue disease (88). In addition, synovial fibroblasts produce high levels of cell adhesion molecules, notably the vascular cell

adhesion molecule-1 (VCAM-1, or CD106). VCAM-1 expression by normal fibroblasts is unusual, because it is typically considered as the cytokine-activated endothelial cell ligand for very late antigen-1 (VLA-4, or $\alpha_4\beta_1$ of the β_1 integrin family). VCAM-1 facilitates the adhesion of monocytes, lymphocytes, eosinophils, and basophils. ICAM-1, which is a major ligand for the leukocyte b2 integrins CD11a and CD11b, is also produced by synovial fibroblasts. These adhesion molecules serve to regulate cell trafficking within the synovium, and the detection of E-selectin and ICAM-1 on normal synovial venules serves to emphasize this function. E-selectin expression is most prominent on small superficial venules in synovium, whereas ICAM-1 is most strongly expressed on larger, deep venules (89). Increased expression of cell adhesion molecules in response to exposure to proinflammatory cytokines

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such as IL-1β and tumor necrosis factor-α (TNF-α) may result in the up-regulation of ICAM-1 and VCAM-1 and the subsequent recruitment of leukocytes during inflammatory conditions. Several members of the CD49 marker group, including integrin receptors for laminin, types I and IV collagens, fibronectin, and vitronectin are also expressed by synovial fibroblasts. The distribution pattern for CD49 expression mapped closely with the occurrence of laminin and collagen IV within the subintima (90).

TABLE 7.1. *Structure, function, and site of expression for cellular markers expressed by synovial fibroblasts*

Marker	Structure	Function	Expression
CD68	110-kd transmembrane Glycoprotein; cell surface and cytoplasmic granules	Unknown	Macrophages Monocytes Lymphocytes
HLA-DR	Covalently bound heterodimers	Antigen presentation	Macrophages Antigen-presenting cells
CD14	GPI-linked glycoprotein	LPS receptor	Macrophages Monocytes
CD11a, b, c	Integrin a chains associated with β_2 integrins	Cell adhesion	Leucocytes

CD16	80-kd transmembrane polypeptide	Low-affinity IgG receptor	Macrophages Natural killer cells
CD64	Fc receptor gRI	High affinity IgG receptor	Macrophages Monocytes
CD54	ICAM-1	Binds to CD11a	Synovial fibroblasts Many tissue types
CD55	DAF	Blocks complement membrane attack	Synovial fibroblasts
CD106	VCAM-1	Binds monocytes and lymphocytes	Synovial fibroblasts Endothelial cells
CD97	G-coupled protein	Activation antigen	Leucocytes
CD49	VLA	Mediate matrix adhesion	Leucocytes

DAF, decay accelerating factor; GPI, glycosylphosphatidylinositol; ICAM-1, intercellular adhesion molecule 1; IgG, immunoglobulin G; VCAM-1, vascular cell adhesion molecule 1; VLA, very late antigens.

Synovial Fluid and Joint Lubrication

Synovial fluid serves multiple roles in the function of the normal joint. It provides nutrients to cells embedded within the cartilage matrix and lubrication to the articulating surfaces of the joint. These functions require a surprisingly low amount of fluid, with an average normal volume of 1.1 mL of fluid and a range of 0.13 to 3.5 mL (91). The control of the normal fluid volume is poorly understood, although the dramatic changes in the properties of the joint fluid during trauma and inflammatory conditions are well recognized. The composition of synovial fluid is similar to that of plasma, but with additional HA, which provides the high viscosity that is characteristic of synovial fluid. HA, a linear, nonbranching polysaccharide, is secreted into the fluid by the fibroblastic cells of the synovial lining and achieves a concentration between 2 and 4 mg/mL (91). HA is a large glycoprotein molecule with an average molecular weight in excess of 1 million daltons, and this molecular size is responsible for the viscous flow characteristics of the synovial fluid. It is thixotropic, in that

the more slowly it flows, the more viscous it becomes (92).

The frictional resistance of animal joints lubricated with synovial fluid can be as low as 0.002, which is one half that of rubber on steel and one tenth that of an ice skate on ice (93). Based on observations regarding the thixotropic character of the fluid, it was originally concluded that joints were lubricated by a hydrodynamic system in which the fluid is held between the bearing surfaces by the continuing rotation of one part of the bearing. Joints are poorly suited to this form of lubrication, however, because they oscillate rather than rotate (36). The finding that the coefficient of friction remains unchanged in joints lubricated with hyaluronidase-treated synovial fluid negated this hydrodynamic theory (94). There are two interfaces within synovial joints that benefit from lubrication: cartilage on cartilage and synovium on cartilage or synovium upon itself. Current hypotheses are that two forms of lubrication are provided by synovial fluid: namely, boundary lubrication, which is a property of surface molecule interactions with the articulating surfaces, and fluid film lubrication, which functions to reduce or prevent contact between the surfaces.

Under physiologic circumstances a thin film of fluid separates two hydrated cartilage surfaces under load. There is ample evidence that this fluid is water “squeezed” from the hyperhydrated cartilage (95). Although the major part of water in cartilage is in the form of a proteoglycan collagen gel (53), it is freely exchangeable with synovial fluid, and a significant portion can be liberated by pressure on the cartilage (96). Because, in the adult, there is little or no traverse of water through the subchondral plate and only modest flow through the substance of the cartilage, the water displaced by cartilage compression is expressed onto the surface of the cartilage, preferentially peripheral to the zone of impending contact. Mow and Mansour (97) have concluded that, under the usual circumstances of joint motion, water tends to be pushed out just in front of the contact area. When the compression is released, the matrix within the cartilage contains enough of a fixed charge to osmotically attract the water and small solutes back into the matrix, and the cartilage regains its original height (98). Thus, the fluid film that exists between moving cartilage layers is made up of the cartilaginous interstitial fluid, which is squeezed onto the surface as the cartilage compresses the synovial fluid already trapped in the contact zone. This mechanism of lubrication is referred to as hydrostatic or weeping (95). Within the zone of impending contact, the lubricating film can be thought of as a squeeze film. The secret of the low friction between the cartilage-bearing surfaces is that they never touch (98). This hydrostatic mechanism clearly functions best under substantial loads, because under small loads, there would be little cartilage compression and little weeping of fluid onto the surface. Physiologically, however, joints frequently move under relatively light load. Under such circumstances, a hydrostatic mechanism would not generate a substantial fluid film, particularly at the moment motion begins.

Boundary lubrication of cartilage on cartilage may be achieved through the interaction of surface-active phospholipids (SAPLs) (99) and the glycoprotein lubricin (100) at the cartilage surface, based on *in vitro* tests in loaded animal joints. Hills has suggested that SAPLs, bound via their polar ends to cartilage, generate an external hydrophobic layer that significantly reduces friction (101). Interestingly, HA may serve to protect this layer through inhibition of phospholipase A2 activity within the joint (102). Lubricin is a 227-kd mucinous glycoprotein that has a high homology with vitronectin and superficial zone protein, and a

lower homology with hemopexin. Lubricin is approximately 50% O–glycosylated with β (1,2,3)Gal-GalNAc and nonuniformly capped with NeuAc (103). It is the product of synovial fibroblasts due to transcription of the megakaryocyte stimulating factor (*MSF*) gene, but appears to be the product of *MSF* exons 6 through 9. Posttranslational modification of the exon 6 product appears to account for the lubricating properties of lubricin, based on latex-glass interface *in vitro* studies (103,104). However, the boundary-lubricating properties of lubricin at the cartilage surface have been challenged and await further research.

The lubrication of synovium on cartilage or synovium upon itself is the result of the affinity of HA for synovial

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surfaces. Thus, HA acts as a boundary lubricant for synovium (105). This is an important component in the ease of motion of joints, because the periarticular soft tissues contribute much more resistance to joint motion than do cartilaginous surfaces (106).

In addition, HA appears to exert a major influence in maintaining the volume of synovial fluid in the joint. HA acts to reduce the volumetric loss that would be expected to occur as fluid pressure increases during joint flexion. This effect has been termed “outflow buffering” by Levick and colleagues (107), and this dynamic resistance to fluid loss may be achieved as a result of the conformation, charge, and osmotic properties of the HA molecules and the ultrafiltration properties of the synovial membrane. As pressure increases, fluid loss is retarded, due to polarized HA accumulation at the interstitial spaces of membrane surface, resulting in elevated osmotic pressure, which retains water molecules within the synovial fluid. HA is resistant to passage through the synovial membrane, due to the formation of large polymer complexes. Polymer interactions between HA and chondroitin sulfate C also appear to enhance the outflow buffering activity (108).

Ligaments, Tendons, and Capsule

Stability for the joint is provided by the joint capsule, tendons, and ligaments. These structures govern the motion of a joint and distribute the forces that impinge on the joint. Ligaments and tendons are classified as dense connective tissue structures and are generally alike in both structure and function. Ligaments form connections between bones, whereas tendons provide the attachment of muscle to bone.

Ligaments consist of collagen fibrils embedded in a proteoglycan matrix sparsely populated with fibroblastic cells (Fig. 7.9). Cells occur in rows in spaces formed between the type I collagen bundles, which form the dominant constituent of the ligament. The rows of fibroblasts interdigitate with processes extending between the collagen bundles. The microfibril may be considered the basic building block of the ligament derived from the properties of the type I collagen molecule, with its helix of three chains (two α_1 and one α_2 chains) aligned together in a quarter stagger pattern, which provides the strength of the assembly. Five collagen I molecules are bound together in the microfibril, and these units are combined to form subfibrils and, subsequently, fibrils. The fibrils are bound tightly together to form the collagen bundle, and this assembly, with fibroblast-filled spaces and proteoglycan matrix, is bounded by the fascicular membrane (109). The insertion of ligaments into bone can be classified as direct or indirect. Indirect insertions are more common and are characterized by Sharpey fibers, which are oblique anchor points for the

deep fibers within bone. Superficial fibers form a contiguous merger directly with the periosteum in indirect attachment. In contrast, the deep fibers involved in direct ligament insertion pass through zones of first uncalcified and then calcified fibrocartilage before integrating with the bone.

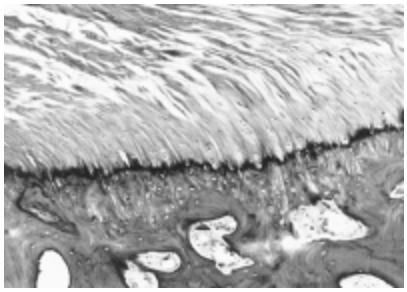

FIG. 7.9. Photomicrograph showing the insertion of a collateral ligament of an interphalangeal ligament into the cortex of the phalanx. Note the parallel bundles of collagen that compose the ligament, becoming first fibrocartilaginous, then calcified, prior to entering the substance of the cortical bond in a fashion similar to Sharpey fibers (hematoxylin and eosin, original magnification × 50).

Although ligaments may be viewed as resistant to force, whereas tendons actively transfer force, they exhibit the same basic structure. Tendons contain a higher ratio of collagen to proteoglycan matrix than ligaments, and the longitudinal alignment of the collagen fibrils is more polarized in tendons. This reflects the variations in directional loading that impinge on ligaments, as opposed to the unidirectional forces that typically are carried by tendons (42). The proteoglycans (notably decorin) interact with the collagen fibrils to increase tensile strength, and may serve to regulate fibril formation. The distribution of different proteoglycans, particularly decorin and biglycan, can effect a change in response to different *in vivo* mechanical forces exerted by the environment. Proteoglycans can improve the resistance to compressive force, such as that generated when tendons wrap around an articular surface (110). In situations of extreme compression without straight-line motion, tendons are usually protected by a sheath that guides the motion path. Sliding within the sheath is aided by the presence of a fluid that is biochemically indistinguishable from synovial fluid and is probably extruded from the synovial membrane (111,112).

Menisci

As previously noted, menisci normally occur only in the knee and temporomandibular, sternoclavicular, distal radioulnar, and acromioclavicular joints. They consist of complete or incomplete flattened, triangular, or somewhat irregularly shaped fibrocartilaginous discs, firmly attached

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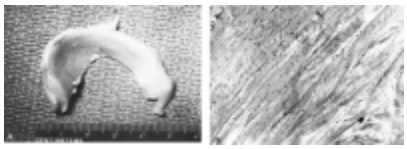
to the fibrous capsules and often to one of the adjacent bones (1,2) (Fig. 7.10).

FIG. 7.10. A: Photograph of a normal human medial meniscus. Note the semilunar shape with a thin free edge and considerably thickened marginal attachment site.



Menisci increase the stability of the joint and serve as weight-bearing structures in the knee. **B:** Low-power photomicrograph of a fibrocartilaginous human medial meniscus. Note the presence of large numbers of parallel bundles of collagen and the sparse cellularity (hematoxylin and eosin, original magnification × 40).

The menisci, like articular cartilages, are for the most part, avascular, but at the site of bony attachment, they usually display a surprisingly rich vascular arcade. No nerves or lymphatics have been identified in meniscal tissues. They presumably derive some of their nutrition from synovial fluid, but also by diffusion from vascular plexuses, which are present adjacent to their attachment to bone or fibrous capsule (42). Examination of the menisci of the knee under polarized or light microscopy has shown that meniscal collagen fibers are arranged circumferentially, presumably to withstand the tensile hoop stresses generated during load bearing (113) (Fig. 7.10B). The fibrocartilage of the meniscus has a biochemical composition considerably different from that of articular cartilage (42,113,114). The water content ranges between 70% and 78%. Inorganic ash accounts for approximately 3% of the wet weight. The remainder of the material, the organic solids, are principally collagen, with type I ($2\alpha_1,1\alpha_2$) predominating (114). Collagen accounts for 60% to 90% of the organic solids (42,115,117). Elastin is present in low concentration (<1%). Proteoglycans constitute less than 10% of the dry weight, and the constituent glycosaminoglycans are principally chondroitin sulfates and dermatan sulfate, with keratan sulfate representing only a minor component (118). Meniscal fibrocartilage appears to have a much more sluggish metabolism than hyaline articular cartilage.

THE JOINT AS AN ORGAN

An organ is a biologic construction of several tissues with a unique and specific function. The diarthrodial joints are organs whose purpose is skeletal articulation. The joints enable us to move our bony frame. The joint is composed of articular cartilage, calcified cartilage, a bony subchondral plate and its underlying cancellous bone, capsule, ligaments, synovial membrane, synovial fluid, and, in some joints, menisci. The muscles, which move and stabilize the joints, can be considered an integral part of the construct. As in any organ, the health and function of the component tissues are interrelated. Biologically, what is critical to the health of the tissues that make up the load-bearing structures of a joint is the stress (pressure or force per unit area) to which they are subjected. Similar compressive stresses can occur in the joints of both the upper and lower extremities. Obviously, larger bearing surfaces are required in the major joints of the lower extremity because the total interarticular forces on them are greater. Furthermore, the load on joints is not constant, because activities are intermittent and often create high peak dynamic loads (119). Frequent rapid starts and equally rapid stops, both of which are associated with high rates of loading, characterize joint motion. It is remarkable that under such potentially punishing mechanical conditions, most joints function throughout the life of the individual without

evidence of destruction of their major load-bearing areas.

Neuromuscular Control

Historically, the synovium was considered to be denervated tissue, since little or no response to mechanical stimulation could be readily detected. However, immunohistologic techniques have revealed the presence of sympathetic efferent fibers and free nerve endings (nociceptors) with unmyelinated C afferent fibers within the synovial tissue (120). The small-diameter postganglionic sympathetic adrenerginic nerve fibers are generally considered to mediate the response of the vasculature to autonomic and chemical stimuli, and thus, control articular blood flow. However, there is evidence

of sensory nerve function in the synovial tissue, with pain responses that can be evoked using hypertonic saline or bradykinin (121). These responses are believed to be mediated via unmyelinated class IV (C) fibers, which are essentially quiescent during normal tissue situations (122). However, these fibers arise from cell bodies in the dorsal root ganglion, where neuropeptides are produced and transported. These neuropeptides, notably substance P, may exert a regulatory role on inflammatory reactions that occur in the joint during arthritic conditions (122,123). In contrast to synovial tissue, the capsule has readily detectable nerve endings that regulate function through proprioreception and maintain the appropriate alignment of the joint to absorb and dissipate the stresses applied during the normal functions of movement (124,125).

Little is known concerning vasoregulation of the sparsely vascularized tendons and ligaments. However, nerve endings in the joint ligaments resemble high-threshold class III (Aδ) cutaneous nociceptors, and sympathetic vasoconstrictor nerve fibers, parasympathetic vasodilator fibers, and small-diameter sensory vasodilator fibers are all present in vessels supplying ligaments and tendons (126). In the meniscus of the knee, nociceptors and mechanoreceptors (Ruffini corpuscles, pacinian corpuscles, and Golgi tendon organ) are distributed throughout the outer body and both the anterior and posterior horns. This distribution is attributed to the requirement for signaling when extreme pressure or tension due to misalignment is exerted on the tissue, evoking mechanical realignment. However, the meniscus may generate proprioceptive information to coordinate movement, velocity, and direction (124).

Biomechanics of Synovial Joints

The mechanical functions of diarthrodial joints require each of the component tissues to play a role in the biomechanics of the joint. Biomechanics is the application of the principles of mechanics, derived from physics and explained through engineering, to the understanding of physiologic function and response. The science of biomechanics examines the forces experienced by a biologic system and the resulting structural, motion, or physiologic responses that occur. In the case of joint function, both the response of the tissues to the load they experience and the motion generated about the joint can be investigated using biomechanics. A joint is a three-dimensional structure and, as such, the forces and responses that it experiences are also three-dimensional. As a result, it is necessary to represent these quantities as vectors. Each vector contains both the

magnitude and directional information regarding the force, deformation, velocity, acceleration, or motion of the system. It is extremely important with vector quantities to define a cartesian coordinate system (x, y, and z axes) and to assign positive and negative directions to each axis. In this way, it is possible to track not only the orientation of a vector, but also its sense—whether a force is pushing or pulling on a point, for example. The type of force that is applied to an object is important in understanding how that material responds. Forces are generally applied to surfaces, and they can act in such a way as to push on that surface (compression), pull on the surface (tension), or slide along the surface (shear).

When it comes to assessing the response and function of a joint, several mathematical relationships are important. The first relate to stress, strength, and strain. Stress is the ratio of an applied force to the area over which it is applied. Strength is defined as the maximum stress that a material can sustain before failure occurs. It can depend on the type of load applied, the direction of the load, and the rate at which the load is applied. Strain is the percentage change in length of an object being squeezed or elongated by an applied stress. Separate strains can be calculated for each direction of applied stress.

For any material, the strain that results from an applied stress is related to that material's properties. For an elastic material, like rubber, the relationship between stress and strain is linear, and the elastic modulus defines the slope of the line relating the two quantities. Elastic modulus is independent of the geometry of the object, but it may vary based on the direction of the applied load, the type of load applied, and the rate at which it is applied. For many materials, the variation of strain with stress is nonlinear, and a single elastic modulus cannot be defined. Secondly, when a material is stretched, it extends in the direction of loading and thins in the perpendicular directions. Likewise, a material that is compressed expands in the directions perpendicular to the loading axis (Fig. 7.11). The Poisson ratio defines this behavior, describing the off-axis response as a percentage of the deformation along the axis of loading. Thus, for a material with a Poisson ratio of 0.3 that is stretched an additional 100% of its original length, the cross-sectional thickness will decrease by 30%.

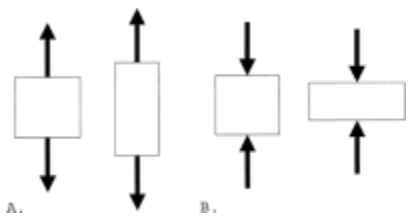


FIG. 7.11. When a load is applied to a piece of material, it deforms both along the axis of the load and perpendicular to it. This behavior is characterized by the material's Poisson ratio.

It can be important to distinguish between the material properties of a material, which are

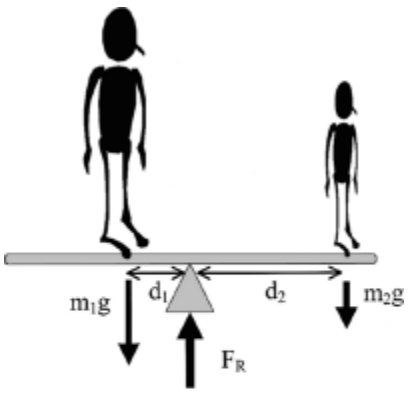
independent of the geometry, and the structural properties, which are dependent on both the material and the geometry. For example, steel can be characterized by its material properties, but

equally important are the maximum forces that can be sustained when the steel is formed into an I beam that will be used for structural support. Thus, the strength of a tissue or organ is not only dependent on its material properties, derived from its extracellular matrix and its chemical composition, but also on how it is put together.

Of equal interest to how materials respond to a force is how an object may move in space. A force will cause an object to move linearly, or translate, but will not cause it to rotate. In order to rotate an object, a moment (a force applied out of line from an axis of rotation) must be applied. When an object or system of objects is moving or stationary and subjected to forces, the overall response and interaction of the forces, moments, and motion are defined based on Newton's Laws. If a system or an object is not moving, it is in static equilibrium.

Static equilibrium is often referred to as a force and moment balance. Although, in three dimensions, this task can be quite complicated, it can easily be visualized using a seesaw example (Fig. 7.12). If the goal is to balance the seesaw in a horizontal position with a mass on each end, the position of each mass needs to be determined. In this example, there are two masses set on the seesaw and a ground reaction force acting through the supporting structure and axis of the seesaw. Each mass results in a force due to gravity equal to the mass times *g*, acceleration due to gravity. In order to be in equilibrium, both the sum of the forces and the sum of the moments must equal zero. Thus, if the two masses are known, the ground reaction force through the seesaw support can be calculated. The reaction force does not cause a moment as it acts directly through the axis, such that the moment arm of the force is zero. As a result, a smaller force (caused by a smaller mass) must be applied farther away from the axis of rotation to balance an applied moment. Or, conversely, if a force is to be applied close to the axis of rotation of a system, it will have to be of a greater magnitude in order to balance existing moments.

FIG. 7.12. The principles of force and moment balance are most simply illustrated through a seesaw. In order for the seesaw to balance horizontally, both the sum of the forces and the sum of the moments must equal zero. *F*, force; *M*, moment; *d*, distance; *m*, mass; *g*, acceleration due to gravity; F_R, ground reaction force.



$$\sum \vec{F} = 0 = F_R - m_1 g - m_2 g$$

$$F_R = g(m_1 + m_2)$$

$$\sum M = 0 = m_1 g d_1 - m_2 g d_2 + F_R(0)$$

$$\frac{m_1 g}{m_2 g} = \frac{d_2}{d_1}$$

Based on these engineering principles and experimental studies, it is possible to determine how a tissue responds when a load is applied to it and to estimate the forces that occur internally within a joint.

The Biomechanics of Joint Function

The joints of the body transfer a substantial amount of load between bones during all daily activities. Although it is difficult to measure these loads *in vivo*, it has been done using instrumented prostheses (5,127) and estimated based on external measurements. On the basis of such data, models have been constructed using the concepts of both static and dynamic equilibrium (3). Muscles act to move or stabilize the bones of the limbs or spine by generating a moment around the axis of rotation of the joint. These internal moments must balance the external forces caused by the weight of the limbs and items being carried, reaction forces from the ground or other supporting structures, and the inertia due to any motion. Because the distance between the insertion point of the muscle and the joint is significantly smaller than the distance between the line of action of any externally applied forces (3), the force generated by the muscle must be substantially larger than the external forces in order to provide the required moment balance. When this muscular force is included in the calculation of the reaction force within the joint itself, joint force estimates typically range from 2.5 to 10 times the weight of the body or body segment that is supported by the joint (5,127,128).

As an example, the forces transmitted down the spine can be examined for an individual standing erect and also while holding a heavy item in front of them (Fig. 7.13). The weight of the torso is generally assumed to be approximately two thirds of the total body weight. In order to maintain an erect posture, the muscles of the posterior spine, primarily the erector spinae, must provide enough force to balance the moments that result from the action of the torso weight and any items being carried at a distance in front of the spine. When

standing erect with arms at the side, the torso weight alone acts through the center of mass of the torso—approximately 10 cm in front of the flexion axis of the spine. For a 75-kg individual, the resulting torso weight (50 kg 3 × *g* = 490 N) creates a moment of 49 N-m tending to flex the spine. In order to balance this moment, the pair

of erector spinae, which acts approximately 3 cm from the flexion axis of the spine, must exert 1,633 N of total force. Then it is important to calculate the total compressive force on the spine, as this will affect pathologies, such as herniated disks, spinal fractures, and low back pain. The reaction force within the spine must balance both the torso weight and the muscle force. In this example, the compressive force that results in the spine is 2,123 N, more than four times the torso weight. When the individual holds a 10-kg mass at arm's length in front of his or her body, this will increase both the muscle moment that must be generated in order to maintain an erect posture and the compressive load experienced by the spine. In this case, the erector spinae must generate 4,083 N of force, and the spinal reaction force is 4,671 N, almost eight times the combination of the torso weight and the carried weight. These interarticular stabilizing forces are far greater than those required for limb motion (3).

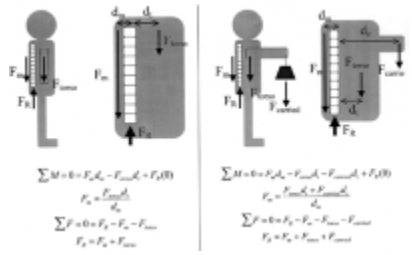


FIG. 7.13. The principles of equilibrium can be used to estimate the muscular and spinal forces that result when the spine supports either only the weight of the torso **(left)** or the additional weight of a carried object **(right)**. F_m, force generated by the erector spinae; F_R, reaction force along the spine; F_{torso}, weight of the torso; $F_{carried}$, weight of the carried object.

This example illustrates the high muscle forces that are required in order to maintain joints in a stable position. Higher internal joint forces result as the distance from an externally applied force to the centerline of the body increases. This is the biomechanical explanation behind recommendations to lift heavy items by bending the knees instead of bending at the back—this keeps the center of gravity of the torso and the item as close to the axis of flexion of the spine as possible.

It is important to remember that the function of a diarthrodial joint is to transfer the load between two adjacent bones during maintenance of posture or limb motion, as well as to allow motion of the parts of the body to occur. In order to do this, most components of the joint must be able to tolerate substantial forces. The subchondral bone and calcified cartilage are subjected primarily to compressive loads through the contact of the joint surfaces. Articular cartilage, on the other hand, sustains both compressive loads (through contact) and shear loads, which result from the motion of the articulating surfaces.

Ligaments apply tensile loads to the bones that they connect, resisting forces that would act to separate the bones. The synovial membrane does not serve a substantial load-bearing role; however, it acts to contain the synovial fluid that both lubricates the joint and, during rapid motion, actually forms a film between the articulating surfaces to separate the cartilage and further distribute the load. The muscles, while not a tissue within the joint itself, play an important role in generating forces that maintain posture and move the limbs, transmitting these loads through tendons to the bones.

Biologic tissues that have mechanical functions respond to their loading environment through changes in their microscopic or macroscopic structure. These changes can either be positive, as tissues adapt to an increased stress environment, or negative, as the loading overwhelms the system and causes tissue degradation. Articular cartilage and

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cancellous bone are both viscolastic tissues, meaning that their matrix contains a substantial fluid phase that is displaced during loading and, thus, absorbs some of the force transmitted. This acts to spare their extracellular matrices. Rapidly applied “impulsive” loads, so fast that the fluid has little time to move, can cause microdamage, which is thought to be a profound trigger for remodeling. As long as the rate of accumulation of microdamage does not exceed the body's ability to heal itself, microdamage is physiologic and can provide a means by which tissue protects itself against future loading. Normal activities subject the tissues of the joint to repetitive, impulsive loading. Substantial damage to the tissue can occur through the resulting accumulation of microdamage if the tissue's ability to heal is overwhelmed by the frequency of this repetitive loading or if the healing processes are impeded as a result of disease or aging.

Injury to one aspect of the musculoskeletal system, whether it is an integral portion of a given joint or simply functioning in the vicinity of the joint, can affect the loading experienced by other tissues in the joints, bones, and muscles. This can initiate a cyclic reaction of tissue adaptation or degeneration that can cause further deviation of physiologic tissue properties and load transfer from the normal state. Thus, it is clinically important to assess the loads on all tissue structures that may result from disease, injury, or clinical intervention. The site-specific changes that occur to the joint in osteoarthrosis are most likely due to these variations in joint loading, be they for anatomic reasons (129) or for neuromuscular control reasons that provoke abnormal, repetitive, impulsive loading (130). However, such determinations are difficult *in vivo*, where they would be most beneficial clinically, due to variations in tissue properties and anatomy between individuals. Novel approaches are now being implemented to determine these parameters by using the experimental data available, as well as more advanced modeling techniques (129).

Biomechanics of Bone

Bone provides the primary structural support for the body. In addition, the relative flexibility of the subchondral bone and underlying cancellous bone is a major factor in allowing for joint congruence under load (131). Failure of these functions will lead to joint failure. Bone is not a simple engineering material, but a living tissue and, as such, it responds to its environment. As a structural material, bone is a composite of organic and inorganic components—namely, collagen and hydroxyapatite. Collagen is a protein with a high tensile

strength and viscoelastic properties, while hydroxyapatite is a calcium phosphate compound with properties similar to that of a ceramic. The needlelike hydroxyapatite crystals, with a size of approximately 0.1 nm, are initially embedded in holes between the collagen fibers and, subsequently, in the intermolecular spaces around the collagen fibers (132). At the tissue level, bony sheets are formed by the parallel arrangement of the reinforced collagen fibers, which in turn, are layered in concentric circles with the collagen fiber orientation varying between layers. The dimension about which these concentric layers of composite, or lamellae, are formed depends on the type of bone involved.

The supporting end of the joint, the epiphysis, is composed mainly of spongy, porous bone referred to as cancellous or trabecular bone. It is formed from a series of interconnected plates, beams, and struts (called trabeculae) that are arranged into a three-dimensional structure that mimics the internal skeleton of a modern skyscraper. The trabeculae are formed from layered or wrapped lamellae and are 150 to 300 μm thick. The beams and plates are generally arranged in the direction of primary loading, whereas the struts provide supporting structures in an off-axis direction in order to minimize buckling. Healthy trabecular bone has an improved strength-to-weight ratio compared with cortical bone—it can carry a substantial amount of load while contributing little added weight to the body. Trabecular bone is found in the metaphyseal and epiphyseal regions of long bones, as well as the inner portions of bones, such as the vertebrae of the spine and the carpal bones of the wrist, and plays an important role in the overall load transfer between bones. The subchondral bone, located directly below the calcified cartilage of an articular joint, is less porous than most trabecular bone and has areas that have remodeled around a central blood vessel (haversian canals).

The mechanical properties of trabecular bone have been extensively characterized, and representative properties are listed in Table 7.2.

TABLE 7.2. *Representative properties of trabecular bone*

Tissue compressive strength (MPa)	0.5–50
Tissue elastic modulus (MPa)	5–150
Material elastic modulus (GPa)	1–11

See references 133 and 134.

Bone is a viscoelastic material, as a result of both the collagen component of the tissue microstructure and the marrow that is part of the bone macrostructure. A viscoelastic material is one in which the material properties are dependent on the rate of loading. The more quickly a load is applied, the stiffer bone will become, which means that bone will deform less under a set amount of load when it is applied quickly than when it is applied more slowly. Of great importance is the fact that, unlike traditional engineering materials, the properties of bone are not constant. The strength, modulus, and density can vary between individuals, between anatomic locations (which can be seen as a variation in response to stress), or as a result of age or disease processes. Variations in the properties of bone may be a function of changes in either the material of the tissue (e.g., the properties of the collagen-mineral composite itself) or the structure of the tissue (e.g., how many trabeculae are present and how they are arranged). In healthy tissue,

the bony material changes only minimally, with the mineral density fairly constant at a level of 1.8 to 1.9 g/cm3 (135) and the mineral to collagen ratio set to about 1:1 by volume. Disease processes can affect the collagen or mineral components of bone and have a profound effect on the underlying properties of the tissue (Fig. 7.14).

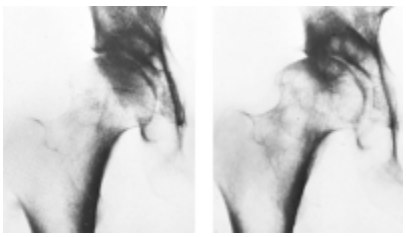

FIG. 7.14. A,B: Radiogram of an osteoarthritic hip that is beginning to sublux laterally. Note the condensation of bone at the lateral rim of the acetabulum and directly across from that area in the femoral head. Where stress is increased above normal, bone becomes sclerotic. If the stress is even greater, cysts will form. Unloaded bone becomes relatively osteopenic.

The reason for the response of bone to age, disease, and body conditions is that it is a living tissue that responds to its physiologic environment. Two basic processes take place in bone as it responds to physiologic demands. Bone modeling occurs primarily in children and young adults and results in bone growth, both in length and in cross-sectional area. The growth of bones through the addition of material to the endosteum (inner wall of the marrow cavity) or periosteum (outer layer of the bone), the result of the modeling process, can also continue throughout life. Bone remodeling involves the removal, and (in general) replacement, of bone. This process allows for the continual recycling of bone, and in healthy tissue it limits the accumulation of microcracks that could lead to fatigue failure of the structure. The same general processes, on a larger scale, are seen in fracture healing (136,137). In loading-related bone remodeling, the changes in bone mass are due to increases or decreases in the structural arrangement of bone, not a change in the amount of mineral per unit volume of collagen at the material level. The three-dimensional structure of trabecular bone develops in response to the primary tensile and compressive loading

axes of the whole bone structure. It has also been suggested that the interconnected plates of subchondral bone, which accurately reflect the stress distribution within the joint, develop so as to provide maximum strength (138).

When a joint is loaded, there is considerable deformation of the epiphyseal and metaphyseal regions, due to the lower stiffness of the subchondral and trabecular bone compared with the cortical diaphysis (131,139). This allows for joint congruence to be maintained (Fig. 7.15). It also allows for a more gradual transition in the stiffness of the loaded tissues in the joint: articular cartilage → calcified cartilage → subchondral and trabecular bone of the epiphyseal/metaphyseal regions → cortical bone of the shaft. This material transition provides for a continuous distribution in the deformation of the overall joint structure and reduces stress concentrations.

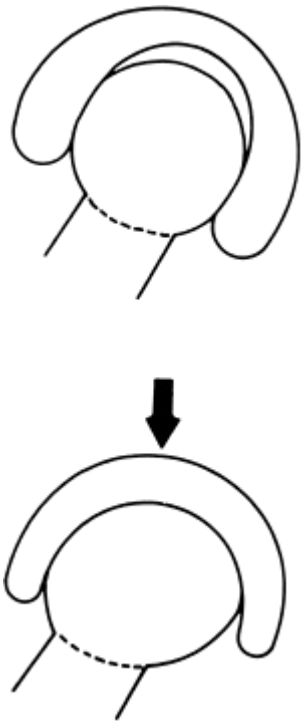

FIG. 7.15. Normally unloaded joints are not completely congruous; under load they become so. It is deformation of the articular cartilage and subchondral bone that allows maximal contact under load. The larger the contact under load, the lower the force per unit area and the consequent stress on these tissues. (From Radin EL, Paul IL, Rose RM, et al. The mechanics of joints as it relates to their degeneration. In: American Academy of Orthopaedic Surgeons. *Symposium on osteoarthritis*. St. Louis: CV Mosby, 1976:41, with permission.)

Biomechanics of Cartilage

Articular cartilage acts as a smooth, low-friction bearing surface between the bones of a joint. It is a water-filled soft tissue composed of a proteoglycan matrix reinforced with collagen. The orientation of the collagen varies through the thickness of the structure, with fibers oriented perpendicular to the articular surface at the deepest level (farthest from the point of joint contact) and parallel to the surface in the uppermost region (37). The collagen fibers of the deep zone provide mechanical continuity between the articular and the calcified cartilage. In the midregion, the apparently random orientation of the fibrous structure actually reorients itself parallel to the loaded surface under compressive load (61). Because collagen fibers are like ropes and cannot support a compressive load along their length, these arrangements provide a great resistance to both the compressive and

shear

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forces experienced by the cartilage. Cartilage is predominantly loaded in compression and is viscoelastic in nature. Under initial loading, the water within the proteoglycan matrix is extruded, and the stiffness of the material is a function of the tissue permeability. In fact, the fluid pressure within the matrix supports approximately 20 times more load than the underlying material during physiologic loading (37). Under extended, noncyclic loading, the collagen and proteoglycan matrix determines the material behavior after the water has been forced from the tissue. Once a load is removed, the charged nature of the proteoglycan molecules produces an osmotic gradient that draws water back into the cartilage, preparing it for future loading. Table 7.3 shows representative values for cartilage properties.

TABLE 7.3. *Representative properties of human articular cartilage taken from the lateral condyle of the femur*

Property	Value
Poisson ratio	0.10
Compressive modulus	0.70 MPa
Permeability coefficient	$1.18 \times 10^{-15} m^4/Ns$

See reference 37.

In addition to providing an optimized articulating surface, cartilage acts with the cancellous bone to improve the fit between the load-bearing, contact surface. This helps to better distribute the load by maximizing the surface contact area (140), preventing stress concentrations from developing in any incongruities that exist in the underlying subchondral bone. Simon and colleagues (141) have shown that cartilage thickness is related to the degree of underlying bony incongruity. Cartilage can be damaged as a result of impacts transmitted through the joints. This typically results in fissures in the tissue that are unlikely to heal. Whether they progress to cartilage loss depends on their location in the

joint—habitually loaded cartilage damage will tend to progress; unloaded damage will not (142,143).

Biomechanics of Ligaments

Ligaments, consisting of a combination of collagen and elastin fibers arranged primarily in parallel along the axis of loading, connect bones to each other across a joint. However, in the unloaded state, the fibers are slightly crimped. As a result, initial tensile loading of the structure acts only to straighten out the component fibers, resulting in a region of low stiffness. Once the fibers have been completely straightened, the individual fiber stiffness dictates the overall structural stiffness. The resulting load deformation curve (Fig. 7.16) exhibits a characteristic low-stiffness toe region followed by a region of increasing stiffness. If loading continues, failure of individual fibers within the structure will result in decreasing overall stiffness followed by rupture. Table 7.4 shows typical values for the tensile properties of ligaments. They are viscoelastic in nature (to an even greater extent than bone) and will fail at lower extensions when loaded at high rates. This behavior explains why a slow stretch will not injure a ligament, whereas a rapid motion may result in rupture. The properties of ligaments vary based on anatomic location, indicating that the properties develop to match the normal physiologic demands.

TABLE 7.4. *Representative properties of ligament under tensile loading as measured for rabbit anterior cruciate ligament with its bony attachments*

Tissue	Property	Value
Ligament	Stiffness (N/mm)	150
	Ultimate load (N)	368
	Energy absorbed to failure (N-mm)	1,330

See references 42 and 109.

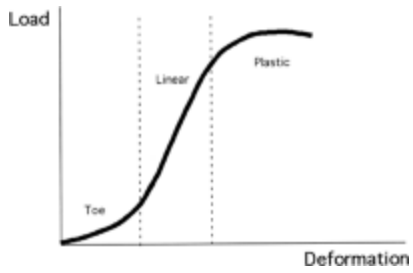

FIG. 7.16. A representative force-deflection curve for a ligament under tensile loading. Notice the first region of very low stiffness, indicative of the straightening of the kinked collagen fibers. This is followed by increasing stiffness as the applied load stretches the parallel fibers of the tissue. Finally, the collagen fibers begin to fail, until final rupture of the ligament body occurs.

Ligaments have a limited blood supply through their insertion sites and only a small population of cells (fibroblasts) within the collagen and elastin fibers. The vascular supply that does exist is necessary for the maintenance of tissue properties. Periods of immobilization, such as occur when a limb is immobilized, result in a decrease in both stiffness and strength in ligaments. The ligament substance can recover in a period of time approximately equal to that of immobilization. However, the strength of the insertion has been seen to reach only 80% to 90% of its original strength after 12 months of recovery following 9 weeks of non-weight bearing (42). Ligaments can be damaged as a result of an excessive load that can rupture some or all of the fibers of the structure. A complete rupture will not properly heal without clinical intervention, because the ligament ends are no longer continuous. Partial ruptures, or sprains,

will heal, but generally over a substantial period of time due to the limited vascular supply to the tissue.

Biomechanics of Muscles

The function of muscles is to exert a tensile force on tendons that connect the muscles to skeletal structures. In this way, the muscles are able to move limbs, stabilize joints, and change the volume of body cavities. The force-generating unit of a muscle is the combination of actin and myosin fibrils that make up a sarcomere. If it is assumed that each pair of fibrils can generate a maximum amount of force, then the maximum load that can be generated by a whole muscle depends on the number of fibrils in a sarcomere and the number of sarcomeres in the muscle as a whole. Thus, the strength of a muscle is nominally related to its volume. Because the length of a muscle is generally determined based on skeletal anatomy, and is not likely to change in an individual after the point of skeletal maturity, variations in muscle strength in an adult individual can be related to the cross-sectional area of the muscle. Muscles with a higher cross-sectional area can produce a greater force.

Muscle is an active tissue; thus, its properties in its passive state contribute little to the function of the skeletal system. Consequently, the innervation of the muscles plays a substantial role in their performance in postural stability and motion. The stabilization function of muscles may be more important to overall posture and motion that the role of muscles in moving the limbs. This is particularly important in the joints without substantial

structural constraint, especially the hip and shoulder. In addition, action of the muscles can act to absorb some of the energy produced by impulse loads through the bones (3).

INTERVERTEBRAL JOINTS

General Structure

The spine is a segmented series of bones that articulate at the intervertebral joints. These joints are composed of two elements: amphiarthrodial, interverterbral disc joints and laterally placed, diarthrodial, interverterbral facet joints. The discs themselves are fibrocartilaginous complexes and separate the vertebral bodies. Motion between any two vertebral segments is limited to a few degrees in any plane by strong ligaments, the amphiarthrodial discs, and the configuration of the intervertebral facet joints, which although diarthrodial, allow little motion. It is the sum of the motion of all of the joints of the entire column that provides the range necessary for the extraordinary mobility of the human spine. Discs from different regions of the spine (cervical, thoracic, and lumbar) vary in size and shape, but are basically identical in their organization (144). The central cartilaginous-like center of the intervertebral discs is constrained on all sides. Its sides are wrapped in a collagenous annulus fibrosus, and its top and bottom surfaces are bordered by the inferior and superior endplates of the adjacent vertebra. (Fig. 7.17).

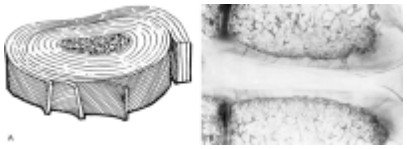

FIG. 7.17. A: Artist's concept of the structure of the intervertebral disc. Note that the concentric layers of the lamina fibrosa show varied orientation of collagen fibers. Centrally placed is the nucleus pulposus, a semifluid mass. **B:** Low-power photomicrograph of the intervertebral disc showing the cartilage plates covering the bony end plates of the vertebral segments. Circumferential rings of fibrous tissue compose the annulus fibrosus, and, in the center, is a poorly staining material, the nucleus pulposus (hematoxylin and eosin, original magnification × 4).

The water content of the nucleus of the disc tends to be even higher than that of articular cartilage. While under sustained loading (such as prolonged standing), some disc fluid does leak out; however, the permeability of the nucleus and annulus to water is substantially lower than that

of articular cartilage. The general confinement of the viscous fluid allows the disc to act as a hydrostatic shock absorber. The role of the spine is axial stiffening while allowing flexibilty in almost all planes of motion: flexion-extension, rotation, and tilting. The stability of the interspinal segments is provided by substantial ligamentous structures that envelop the bony parts. Where the ligaments are not continuous, posterolaterally, is where disc herniations occur. The stability of the spinal column is provided by the interspinal muscles,

which are substantial and can generate a large force. Paralyze these muscles, and the patients cannot sit or stand without external support (145). The biomechanics of the spine are addressed in the ensuing paragraphs.

As far as the detailed anatomy is concerned, the annulus fibrosus consists of a ring of fibrous lamellae that encases the nucleus and unites the vertebral bodies. This unification is achieved by creating contiguity of the fibrous structure with the margins of the vertebral segments and the investing anterior and posterior longitudinal ligaments (1,144). The fibrous layers of the annulus are approximately 20 μm thick and, on polarized microscopic examination, are organized such that alternating sheets of collagen are set at an angle to each other (146,148). Some flexibility is achieved by random arrangement of the fibers (0.1–0.2 μm in diameter) within the substance of the plates of collagen and by a relatively high proportion of proteoglycan and interstitial fluid in the annulus as compared with the more rigid tendons or ligaments (128,149,150). The annulus is not uniformly thick throughout the structure. The plates in the anterior third of the disc are thickest and most distinct; those in the posterior aspect are more closely packed and somewhat thinner (151).

The second component of the disc is the nucleus pulposus, which occupies the central portion of the disc and is surrounded by the annulus. Actually, the nucleus is not centrally placed within the confines of the annulus, but during erect posture usually lies closer to the posterior margin of the disc (151). The nature of this material and its function in the joint are most evident when, on transverse or sagittal sectioning of the disc, it is found to bulge prominently beyond the plane of the section. The nucleus consists of a viscid fluid structure, which, histologically, is sparsely cellular and consists principally of loose, delicate, fibrous strands embedded in a gelatinous matrix (7). In the central portion of the nucleus, the fibers appear randomly distributed, but as they approach the superior and inferior cartilage plates, they assume an oblique angular orientation to become embedded in the cartilage at the peripheral attachment of the nucleus (146,151,152). The structural interspace between the nucleus and the annulus is difficult to appreciate, and in many older subjects, the two tissues blend imperceptibly (144,146).

The disc is contained superiorly and inferiorly by cartilaginous plates, which are firmly fixed to the bony endplates of the adjacent vertebral segments and differ little in structure from the hyaline articular cartilage seen in diarthrodial joints, except that they have no collagenous “skin,” or any discrete superficial surface (144,151). Instead, the cartilage serves as an anchor for the fine filamented fibers of the nucleus pulposus in its central portion and the coarse fibrous plates of the annulus fibrosus peripherally.

Embryology and Development

The development of the intervertebral disc in humans occurs early in fetal life. Following formation of the morula, the mass of primitive cells becomes the blastocyst, which rapidly undergoes proliferation and differentiation into ectoderm and endoderm, which, in turn, combine to form the embryonic disc (153). A primitive streak develops at the caudal end of the dorsum of the embryonic disc. The groove deepens, and at the most caudal portion the primitive node develops. At this site, cells arising from the mesoderm give rise to the notochord, which thickens and rolls up into the neural folds to form the neural tube (154,155). The mesodermal tissues on each side of the notochord form the primitive

somites, and, at approximately the third week of gestation, distinct spinal segments can be identified. The central portions of the somite on either side of the notochord form the vertebral column. Mesodermal cells from each side join to form the vertebral bony elements, including not only the cartilaginous endplates, but also the annulus fibrosus and the peripheral portions of the nucleus pulposus (153). The notochord, which originally lies centrally placed in the vertebral body and disc, is compressed as chondrification of the vertebra progresses and, within a short time, is destroyed (155). No notochordal remnants can be found in the vertebral body in the mature fetus or adult (except in an occasional patient who develops a chordoma). The portion of the notochord that lies in the intervertebral disc area, however, becomes the major central portion of the nucleus pulposus (155). The annulus develops early in embryonic life from the densely aggregated cells about each pole of the somitic segment and eventually surrounds the notochord completely. Ossification begins in the vertebral body at the 50- to 60-μm stage (third month) as vessels invade the cartilaginous precursors, but the endplates remain cartilaginous and serve as the attachment site for the adult nucleus pulposus and annulus fibrosus (156).

Biochemistry

The annulus fibrosus is principally collagenous but is relatively hyperhydrated compared with other fibrous tissues, with water estimates ranging between 65% and 70% (148,150). Collagen accounts for approximately 50% to 55% of the dry weight. The remainder of the tissue consists of proteoglycan and the principal glycosaminoglycans, including chondroitin sulfate and keratan sulfate (157,158). A small amount of glycoprotein is present (129,130,159). The nucleus has a much higher water content than the annulus,

with estimates for immature animals as high as 88%. The value decreases to about 65% in elderly individuals (126,131,148). Collagen is also present in the nucleus (mostly type II), but accounts for a considerably smaller percentage of the dry weight (20%–30%) than in other joint connective tissues (55,58,59,148,157). Most of the material within the nucleus consists of proteoglycan (149,160,162) and other, as yet poorly defined, proteinaceous materials (159). The distribution of glycosaminoglycans varies considerably, depending on the age of the patient and the amount of degeneration that has occurred, but chondroitin 6-sulfate (~40%), chondroitin 4-sulfate (5%), keratan sulfate (~50%), and hyaluronic acid (<2%) have all been reported (157,158). Pearson and coworkers (159) have described the presence of other proteins, probably glycoproteins, that are believed to be important in maintaining the physical properties of the material. Lysosomal enzymes have been described that presumably play a role in the normal turnover of the proteoglycans (147). Synthetic activity takes place in the outer ring of cells of the nucleus (163).

Function and Biomechanics of the Intervertebral Disc and Spine

The main role of the intervertebral disc is to serve as a load-bearing structure and absorb energy during the compression of the spine (164,166). The resistance to compressive axial loading, one of the predominant mechanisms of spinal force transmission, is mediated through the compressibility of the hyperhydrated nucleus. The nucleus pulposus, in

conjunction with the surrounding annulus fibrosus, resists and modifies pressures by “barreling” (losing height while gaining in width) (164,166,167). The application of a force to the disc compresses the nucleus pulposus, which causes the intradiscal pressure to increase and creates a tensile force in the annulus fibrosus. The annulus is designed to absorb most of the barreling of the disc by collagen network stretch.

If an articulated spine is loaded with the weight of a human head, it will buckle. Muscle action is required if the spine is to maintain an erect position (16). These muscle-produced loads on the spine during normal daily activities are thus necessarily higher than body weight, reaching as high as eight times the total supported weight for even a small load carried in front of the body. The spine consists of vertebral bodies and intervertebral discs arranged in series. As a result, a load applied to the end of the spine will result in the same applied force at each level. In reality, the load carried by the vertebrae and discs in the lumbar spine are higher than those of the cervical and thoracic regions, due to the increased percentage of body weight located above each level of interest; spinal loading increases in the caudal direction.

If a healthy spine is loaded in pure compression or compression plus flexion within normal physiologic limits, failure will occur in the vertebral bodies before significant damage occurs to the discs. Rupture of an intervertebral disc requires a combination of compression, flexion, and rotation. Under these circumstances, tearing of the annulus begins at its periphery (164). The biochemical changes associated with aging of the nucleus pulposus would appear to play little role in intervertebral disc rupture (168).

Integrity and congruence of the intervertebral facet joints require the maintenance of the intervertebral disc space. Loss of disc height from rupture and extravasation of disc material, digestion of the nuclear proteoglycans, or surgical excision of the disc will lead to intervertebral space collapse and settling of the intervertebral facet joints, resulting in articular incongruity with diminution of their contact areas (169,170). The disc should not be considered as a separate unit, but rather as an integral part of the intervertebral joint that includes the facet joints and the anterior and posterior longitudinal ligaments. All of these components act together to maintain the axial resistance to compression and stability of the spine (165,171).

HEALING OF SYNOVIAL JOINTS

There is consensus that all the tissues of the joint, except cartilage, can heal. All but cartilage are vascularized and can participate in the usual inflammatory healing phenomenon. In addition, the cells in mature cartilage have limited mobility and are a poor source of cells for healing. But, under certain circumstances, cartilage does heal. The controversy surrounding the healing of articular cartilage is due to the several variables which affect such repair. Articular cartilage repair requires a source of cells, hydrostatic pressure, and physiologic tissue pressures. It initially heals as fibrocartilage and, if that survives, over time, has been reported to mature to hyaline cartilage (172). The cells that heal cartilage come from the synovium or subchondral bone and healing requires motion and reasonable intraarticular pressures (173). Such repair is initially fibrocartilaginous in nature (172,174). There are reports of fibrocartilage evolving over may years to hyaline cartilage (172). The frequently short life of fibrocartilage would appear due to mechanical

factors and the difficulty it has bonding with the remaining articular cartilage (172,175). If congruity remains or can be reestablished and the stress concentrations removed, joints can functionally heal, as Pauwels, Coventry, Maquet, and others have shown (172). Meniscal fibrocartilage can undergo repair if the damage is peripheral, in the zone of vascularization (176).

SUMMARY

The major function of the joint is to allow movement of the skeletal frame, which requires transmission of the significant forces generated by muscle action and body

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weight. Joints are designed to move easily. As in any organ, several tissues play a cooperative role. The articular cartilage and synovial membranes act as lubricating surfaces, both tissues supplying the lubricant. Underlying the articular cartilage is a complicated arrangement of subchondral bone, designed to minimize intraarticular pressure while still allowing transmission of the interarticular load from one bone to the next. The ligaments act mechanically and as proprioceptive sensors to help guide the joint's motion. The muscles control joint movement and act as shock absorbers to dampen impulsive loads. The health of the organ depends on the interrelationship of these various tissues, and failure of one can lead to eventual failure of the whole organ. As discussed in this chapter, the biologic and mechanical factors acting on joints are inseparable. One must understand the relationship between the two to appreciate the physiology of this organ.

In this chapter we have stressed the increased interest in the molecular biology of the tissues of the joint and its relationship to biomechanics. The biphasic model of articular cartilage is still being revised and has become critical for “molecular level” modeling of articular cartilage replacement and predictions of chondrocyte deformation (177). There is finally acceptance that, for the best results, joint structures must be transplanted immediately after injury before remodeling occurs (178) and that establishing proper tension of anterior cruciate ligament grafts is critical for a successful clinical outcome (179). In these days of increasingly aggressive surgical approaches as regards osteoarthrosis, the *Journal of Bone and Joint Surgery* has seen fit almost 50 years later to republish Wally Blount's 1956 editorial, “Don't throw away the cane” (180). We should all be attentive to the lessons of history.

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