Why Do Some Intervertebral Discs Degenerate, When Others (in the Same Spine) Do Not?

Article *in* Clinical Anatomy · April 2014

Impact Factor: 1.33 · DOI: 10.1002/ca.22404

4 authors:

Michael A Adams
University of Bristol
187 PUBLICATIONS **9,263** CITATIONS
SEE PROFILE

Dr. Polly Lama
McGill University
16 PUBLICATIONS **62** CITATIONS
SEE PROFILE

Uruj Zehra
University of Bristol
15 PUBLICATIONS **27** CITATIONS
SEE PROFILE

Patricia Dolan
University of Bristol
146 PUBLICATIONS **5,990** CITATIONS
SEE PROFILE

Clinical Anatomy 00:00–00 (2014)

REVIEW

Why Do Some Intervertebral Discs Degenerate, When Others (in the Same Spine) Do Not?

MICHAEL A. ADAMS,* POLLY LAMA, URUJ ZEHRA, AND PATRICIA DOLAN

Centre for Comparative and Clinical Anatomy, University of Bristol, United Kingdom

This review suggests why some discs degenerate rather than age normally. Intervertebral discs are avascular pads of fibrocartilage that allow movement between vertebral bodies. Human discs have a low cell density and a limited ability to adapt to mechanical demands. With increasing age, the matrix becomes yellowed, fibrous, and brittle, but if disc structure remains intact, there is little impairment in function, and minimal ingrowth of blood vessels or nerves. Approximately half of old lumbar discs degenerate in the sense of becoming physically disrupted. The posterior annulus and lower lumbar discs are most affected, presumably because they are most heavily loaded. Age and genetic inheritance can weaken discs to such an extent that they are physically disrupted during everyday activities. Damage to the endplate or annulus typically decompresses the nucleus, concentrates stress within the annulus, and allows ingrowth of nerves and blood vessels. Matrix disruption progresses by mechanical and biological means. The site of initial damage leads to two disc degeneration "phenotypes": endplate-driven degeneration is common in the upper lumbar and thoracic spine, and annulus-driven degeneration is common at L4-S1. Discogenic back pain can be initiated by tissue disruption, and amplified by inflammation and infection. Healing is possible in the outer annulus only, where cell density is highest. We conclude that some discs degenerate because they are disrupted by excessive mechanical loading. This can occur without trauma if tissues are weakened by age and genetic inheritance. Moderate mechanical loading, in contrast, strengthens all spinal tissues, including discs. Clin. Anat. 00:000–000, 2014.

Key words: intervertebral disc; degeneration; ageing; injury; review

INTRODUCTION

Intervertebral disc degeneration has been described as a genetically determined disorder (Battie and Videman, 2006) that is "constitutional" in the sense that it can hardly be distinguished from "normal" ageing (Haefeli et al., 2006). This viewpoint has important medico-legal implications, but it raises several problems. Within a given spine, why should some discs degenerate so much more than others that share the same age, genetic inheritance, and internal environment? And why do certain regions of degenerated discs (such as the postero-lateral annulus) usually show more advanced changes than other regions? The purpose of this review is to distinguish "disc degeneration" from ageing, and to explain why certain discs degenerate rather than age normally.

*Correspondence to: Professor Michael A. Adams, Centre for Comparative and Clinical Anatomy, University of Bristol, Southwell Street, Bristol BS2 8EJ, UK. E-mail: M.A.Adams@bris.ac.uk

Received 6 December 2013; Revised 4 March 2014; Accepted 1 April 2014

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/ca.22404

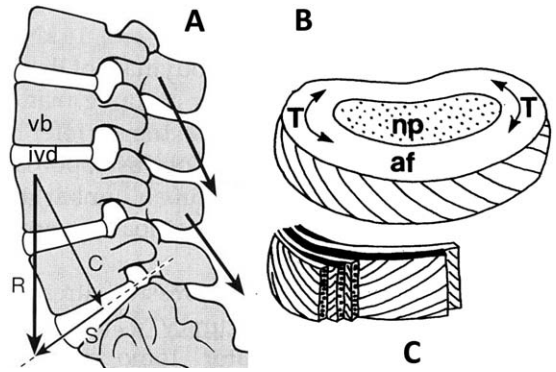

Fig. 1. **A**: Human lumbar spine showing intervertebral discs (ivd) lying between vertebral bodies (vb). Anterior on left. Gravitational forces, and muscle forces acting on the neural arches (arrows), can be summed to form a resultant force (*R*), which has a component (*C*), which compresses the disc, and another (*S*), which shears it. **B**: Oblique diagram of an intervertebral disc. The nucleus pulposus (np) behaves like a pressurized fluid, and is restrained by tensile "hoop stresses" (*T*) in the surrounding annulus fibrosus (af). **C**: Expanded cut-away of annulus, showing the alternating collagen fiber direction in adjacent lamellae. Compare with photographs in Figure 4. [Adapted from Adams et al. The Biomechanics of Back Pain (3rd Edition), 2013, Churchill Livingstone, reproduced by permission].

INTERVERTEBRAL DISC STRUCTURE AND FUNCTION

Gross Anatomy

Intervertebral discs comprise a soft central nucleus pulposus surrounded by 10–20 concentric lamellae of the annulus fibrosus (Fig. 1). The nucleus is a hydrated proteoglycan gel held together by a loose network of collagen Type II fibrils, which can be visualized using scanning electron microscopy (Iatridis and Ap Gwynn, 2004). These fibrils resist large tissue deformations, and coalesce in places to provide firm attachments to the surrounding annulus and cartilage endplate (Wade et al., 2012). Each lamella of the annulus contains parallel arrays of coarse collagen Type I fibers within a sparse proteoglycan gel. Fiber direction is orientated at ~60° to the long axis of the spine, and alternates in successive lamellae (Fig. 1C). Adjacent lamellae are joined radially by discrete translamellar bridging fibers (Schollum et al., 2009), which bind together collagen fiber bundles of adjacent lamellae in a similar manner to logs that are strapped together to form a raft (Fig. 2).

Endplates

Discs are separated from the vertebral bodies above and below by "endplates," which comprise a thin layer of hyaline cartilage bonded to an even thinner layer of perforated cortical bone (Fig. 3). The bone layer contains many pores, typically 140–390 μm in diameter (Rodriguez et al., 2012). Pores tend to be greater and more plentiful in central regions of the endplate, opposite the disc nucleus, and they are sufficiently large to allow free passage of metabolites between the vertebral bone marrow and the nucleus.

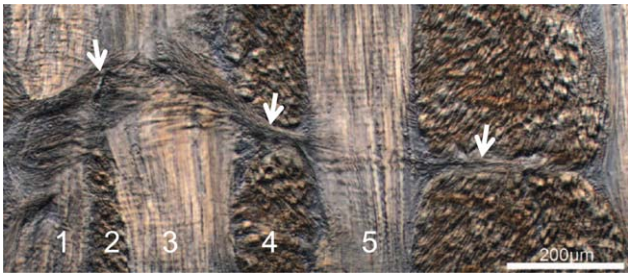

Fig. 2. A "translamellar bridging network" (arrows) binds lamellae together in the annulus. Ovine annulus fibrosus is viewed in an oblique plane using differential interference contrast microscopy (Schollum et al., 2008). Even-numbered and odd-numbered lamellae have collagen fibers approximately perpendicular to and parallel to (respectively) the plane of the image. (From Schollum et al., Spine 2008, 33, 2702–2710, reproduced by permission). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

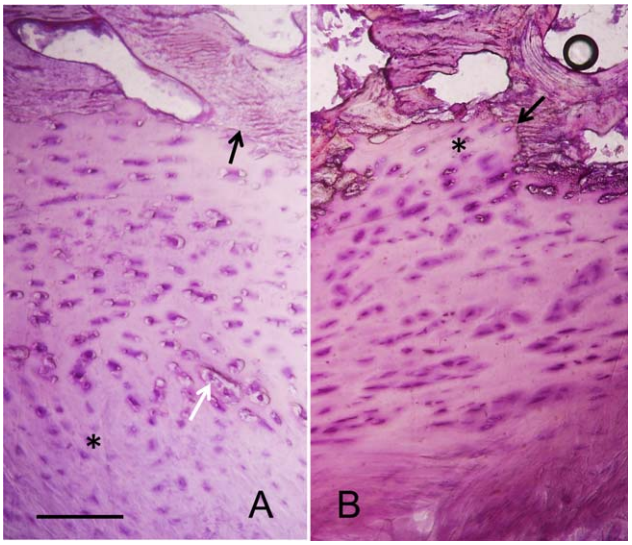

Fig. 3. Intervertebral discs join the vertebral bodies at the endplates. **A**: In this undamaged tissue (female 74 yrs), there is a straight junction between the hyaline cartilage endplate and the bony endplate above it (black arrow), and a gradual transition from the cartilage endplate to the annulus fibrosus below (*). There are some small calcified areas within the cartilage (white arrow). **B**: In this degenerated disc, the bony endplate has a step fracture (arrow), but the defect is filled by the hyaline cartilage endplate (*), and there is no growth of blood vessels into the disc. (H & E staining; bar = 100 μm.). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

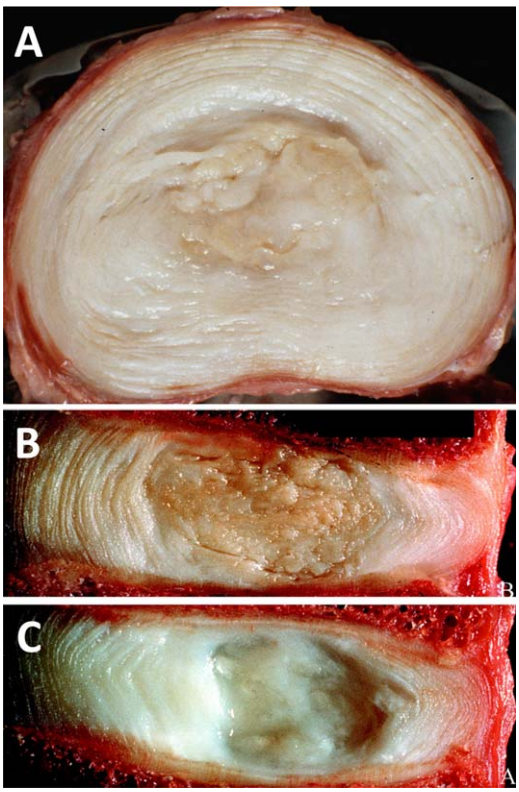

Fig. 4. **A**: Middle-aged, nondegenerated human lumbar intervertebral disc sectioned in the transverse plane, showing typical signs of ageing, but not degeneration (anterior on top). **B**: Similar disc to that shown in A, sectioned in the mid-sagittal plane (anterior on left). **C**: Young nondegenerated lumbar disc sectioned in the mid-sagittal plane. [From Adams et al. The Biomechanics of Back Pain (3rd Edition), 2013, Churchill Livingstone, reproduced by permission]. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The cartilage endplate, which adheres to the bone on the disc side, comprises a layer of hyaline cartilage, ~1 mm thick, which is thickest adjacent to the inner annulus, thins toward the nucleus, and is very thin or absent near the peripheral annulus (Moon et al., 2013). The cartilage endplate is much less porous and permeable than the underlying bone (Rodriguez et al., 2011), especially when it is compressed by a high hydrostatic pressure (Ayotte et al., 2001), so that it serves both as a biological filter and as a means of maintaining the water content and pressure within the nucleus when the disc is compressed.

Discs Allow Movement and Distribute Load

Intervertebral discs are too stiff to function as efficient shock absorbers, but they are soft enough to allow small intervertebral movements in bending and axial rotation, and normally spread compressive loading ("C" in Fig. 1A) evenly on to the adjacent vertebral bodies, even when the spine is flexed or extended (Adams et al., 2000b). The high water content of the nucleus causes it to act as a pressurized fluid (Adams et al., 2000b), which is constrained by tension in the surrounding annulus. When the spine is loaded vigorously, nucleus pressure causes the vertebral endplates to bulge into the vertebral bodies (Brinckmann et al., 1983). Human discs are protected by the neural arch from excessive anterior shearing forces, axial rotation, and backwards bending (Adams et al., 2013). The neural arch also resists a variable proportion of the compressive force acting down the long axis of the spine: depending on posture and on disc height (which is influenced by degeneration and time of day) the neural arch resists 20–90% of the compressive force (Pollintine et al., 2004).

METABOLIC PROBLEMS IN AGEING CARTILAGE

Lack of a Blood Supply

Both hyaline and fibrocartilage are distinguished by a high concentration of proteoglycan molecules in their extracellular matrix. Proteoglycans inhibit the ingrowth of blood vessels (Johnson et al., 2005) and nerves (Johnson et al., 2002). They also attract water, giving rise to a compressive turgor, which in loaded tissue, manifests as a high physical pressure, which is sufficient to collapse any blood vessels within it. Consequently, cartilage becomes avascular and aneural in early childhood, as the skeleton becomes weight-bearing. Metabolite transport difficulties intensify as cartilaginous structures grow, causing cell density to decrease steadily up until skeletal maturity (Meller et al., 2009; Liebscher et al., 2011). The fibrocartilaginous intervertebral discs are worst affected because they are the largest avascular structures in the body (Maroudas et al., 1975). Problems are most severe in the nucleus, where cell density falls to ~4000 mm^3 in adults (Hastreiter et al., 2001).

Adaptation and Healing

Cartilage cell density does not normally decline after skeletal maturity (Liebscher et al., 2011), and the small cell population appears well adapted to the anaerobic conditions that arise from poor metabolite transport (Bibby et al., 2005). Matrix turnover is very slow, but measurable (Sivan et al., 2008), and comparisons between the mechanical properties of human disc tissues and their adjacent vertebrae suggest that discs are capable of limited adaptation to mechanical demands (Skrzypiec et al., 2007). However, the extremely low cellularity of adult cartilage creates problems if it is injured. In surgically injured sheep discs, effective healing is observed in the outer annulus but not in the nucleus or inner annulus (Osti et al., 1990). In adult humans, the outer annulus has four times the cell density of the nucleus (Hastreiter et al., 2001), suggesting that it may have some ability to heal (Adams et al., 2010).

AGE-RELATED CHANGES IN INTERVERTEBRAL DISCS

The following discussion will focus on intervertebral discs, but much of it is applicable to articular cartilage also (Temple et al., 2007).

Cell Senescence

Although disc cell density does not normally decline after skeletal maturity, an increasing proportion of cells in old discs become "senescent" in the sense that they exhibit shortened DNA telomeres, which reduces their ability to replicate (Le Maitre et al., 2007).

Ageing of the Extracellular Matrix

Reduced cell vitality affects the surrounding matrix. Some proteoglycan molecules become fragmented and are lost from the tissue, reducing tissue hydration, especially in the nucleus (Antoniou et al., 1996). As a result, disc height typically reduces by 0.6% per year in middle-aged men (Videman et al., 2008a). Reduced hydration creates stress concentrations (Adams et al., 1996a), which inevitably weaken the matrix. In addition, collagen "turnover" becomes slower (Sivan et al., 2008), allowing increased levels of collagen crosslinking; in particular nonenzymatic glycation (NEG) occurs as matrix proteins become increasingly crosslinked with sugars. NEG can be recognized from the typical brownish appearance of the ageing tissue (Figs. 4A and 4B), but its most important effect is to make cartilage more brittle and vulnerable to injury (DeGroot et al., 2004). Coarse collagen Type I fibers become more abundant and encroach on the nucleus, reducing its size. Generally, there is no blood vessel or nerve infiltration (Palmgren et al., 1999).

Age-Related Changes in the Endplate

The bony endplate becomes thinner and more porous with age, reflecting systemic osteopenia in many older people, and increasing the overall permeability of the endplate (Rodriguez et al., 2012). This is consistent with previous work showing that the number of very small (20–50 μm) pores in the endplate decreases with age and disc degeneration, as the number of larger holes increases (Benneker et al., 2005). The central endplate often bulges more into the vertebral body (Fig. 5), presumably as a result of focal defects and (possibly) of "creep" deformation of undermineralized bone (Pollintine et al., 2009). The cartilage endplate also thins with age, and shows signs of NEG. Porosity and permeability increase steadily with age, both in the cartilage and bone layers (Rodriguez et al., 2011), but typically there is no blood vessel or nerve ingrowth into the disc (Fig. 3).

Impaired Function in Old Discs

Loss of proteoglycans and water reduces nucleus pressure. In addition, stiffening of the annulus due to increased collagen crosslinking and NEG causes it to resist compression more strongly. These effects combine to cause a shift in load-bearing from nucleus to annulus (Adams et al., 1996b) and from the disc (overall) to the neural arch (Pollintine et al., 2004). The outer annulus weakens (Skrzypiec et al., 2007), presumably because of accumulating minor defects, including circumferential splits between lamellae. In the wedge-shaped L4-L5 and L5-S1 discs, compressive stresses become concentrated in the posterior annulus, especially in erect (upright) postures (Adams et al., 1996b). This is probably because the reduced height of the posterior annulus at these levels does not allow it to deform vertically as much as the taller anterior annulus, and so it becomes more severely loaded as nucleus pressure and height decrease.

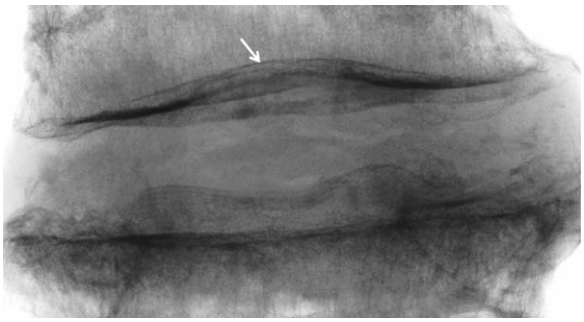

Fig. 5. Micro-CT scan in the frontal plane of an old cadaveric intervertebral disc and adjacent bone, showing how the bony endplate typically deforms into the adjacent vertebral body. In this specimen (female, 93 yrs) the smooth curves (arrow) suggest time-dependent "creep" deformation of bone rather than fracture.

DEGENERATIVE CHANGES AFFECT SOME INTERVERTEBRAL DISCS

What is Disc Degeneration?

Disc degeneration has traditionally been graded on scales (e.g., 1–4) according to the presence or absence of specific features (Adams et al., 1986; Thompson et al., 1990), some of which refer to structural changes such as endplate defects, annulus fissures, and annulus collapse. Unfortunately, some milder "features" refer to biochemical changes, which are present in all old discs, creating confusion over what really constitutes "degeneration," and how it might be distinguished from ageing. In 2006, Adams and Roughley suggested that intervertebral disc degeneration should be defined as "an aberrant, cell-mediated response to progressive structural failure," and that a degenerate disc is one with "structural failure combined with accelerated or advanced signs of ageing" (Adams and Roughley, 2006). The term "degenerative disc disease" should be reserved for a degenerated disc, which is also painful. According to this scheme, which has been widely cited, some discs degenerate because they are so weakened by age, and by an unfavorable genetic inheritance (Battie et al., 2008), that they sustain damage during normal

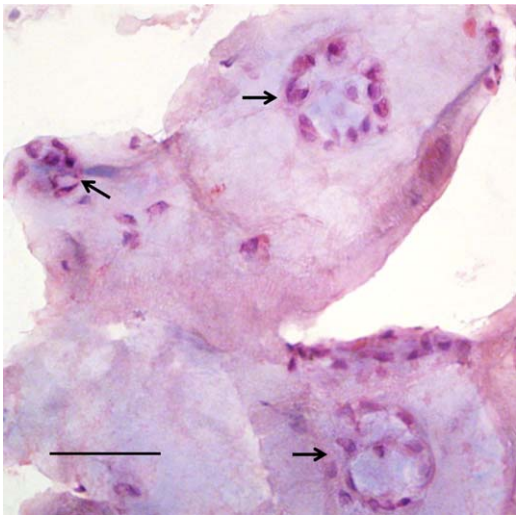

Fig. 6. Cell clusters (arrows) are common in degenerated intervertebral discs. This thin section of inner annulus fibrosus is from a degenerated human lumbar disc removed at surgery for suspected discogenic back pain. Note the disrupted matrix, which is almost acellular apart from the clusters. (H & E staining; bar = 50 μm.). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

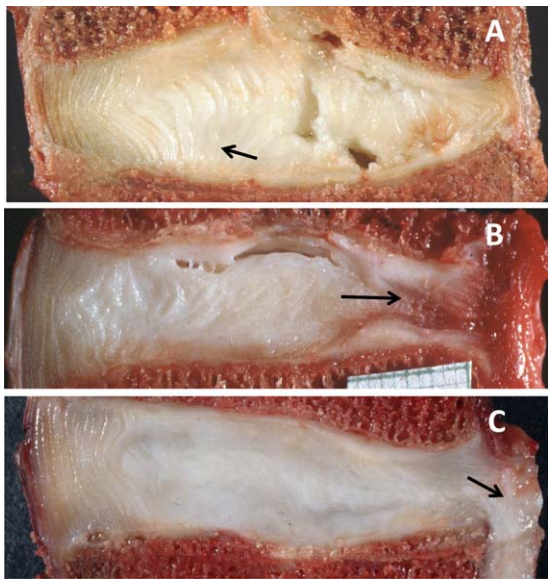

Fig. 7. Degenerated human lumbar discs sectioned in the mid-sagittal plane (anterior on left). **A**: In "endplate-driven degeneration," a bony endplate is fractured, and the annulus is internally disrupted (arrow). **B**: "Annulus-driven degeneration" involves direct damage to the annulus: in this case, a complete radial fissure (arrow) allows nucleus tissue to move peripherally, and blood to move centrally. **C**: Herniation of nucleus pulposus down a radial fissure in response to severe mechanical loading (From Adams et al., Spine, 2000a, 25, 1625–1636, reproduced by permission). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

every-day activity. In degenerated discs, abnormal cell signaling (Shamji et al., 2010), elevated enzyme activity (Antoniou et al., 1996; Weiler et al., 2002), and cell clustering (Fig. 6) are all consistent with attempted repair. It is sometimes suggested that discs degenerate because of altered cell signaling, or because of impaired regulation of matrix-degrading enzymes, but this surely is "putting the cart before the horse?"

Patterns of Structural Damage to Intervertebral Discs

Circumferential tears or splits between lamellae in the annulus affect all lumbar discs by the age of 40 yrs (Haefeli et al., 2006). Less common are radial fissures (Haefeli et al., 2006), which progress from the nucleus to the outer annulus, usually posteriorly or posterolaterally (Fig. 7B), and which can sometimes allow nucleus material to herniate within or through them (Adams and Hutton, 1985). Vertebral endplates often show signs of fracture (Fig. 7A), sometimes accompanied by vertical herniation of disc material into the vertebral body. Inwards bulging or collapse of the inner annulus (Fig. 7A) is also common (Gunzburg et al., 1992). All of these structural changes can be created by severe or repetitive mechanical loading in cadaveric and animal tissues (Adams et al., 2013), but in living people, they may develop over much longer timescales (see below).

Two Disc Degeneration "Phenotypes"

The course of disc degeneration depends on whether the initial structural defect involves the endplate or annulus. Damage to a vertebral endplate causes an immediate and large loss of pressure in the nucleus, and high stress concentrations arise in the annulus, especially posterior to the nucleus (Adams et al., 1996b, 2000a). These effects are especially large in lower thoracic and upper lumbar discs (Dolan et al., 2013), and they can cause the annulus to collapse into the decompressed nucleus as shown in Figure 7A (Adams et al., 2000a; Holm et al., 2004). Nucleus decompression also impairs matrix synthesis by nucleus cells (Ishihara et al., 1996), and high stress concentrations in the annulus increase the expression of matrix-degrading enzymes (Handa et al., 1997). In this way, endplate damage drives disc degeneration by biological as well as mechanical means (Adams et al., 2009).

Alternatively, the annulus can be disrupted directly by high or repetitive loading in bending and compression. This type of loading occurs typically during heavy lifting activities (Dolan et al., 1994) and can cause the nucleus to herniate into (or through) the stretched region of annulus (Adams and Hutton, 1982, 1985) as shown in Figure 7C. Disc herniation (or prolapse) occurs most readily in lower lumbar discs in the age range 40–50 yrs (Adams and Hutton, 1982) but cervical disc herniation is also common. Injuries to the annulus have less effect than endplate damage on

nucleus pressure or metabolism (Przybyla et al., 2006). Nevertheless, they can cause a variety of degenerative changes in the annulus, including disc cell apoptosis and enzymatic degradation of the matrix (Walter et al., 2011). Most of the "degenerative" changes found in herniated disc material removed at surgery probably occur after the herniation takes place, as a result of tissue swelling, leaching of proteoglycans, and revascularization (Lama et al., 2013). Recent developments suggest that herniating disc tissue often pulls some cartilage endplate away from the subchondral bone (Rajasekaran et al., 2013), allowing free communication between disc and vertebral body. This can lead to inflammatory ("Modic") changes in the endplate, and bacterial infection in the disc (Albert et al., 2013a).

The initial injuries in endplate-driven and annulus-driven degeneration are more likely to occur if the disc has a substantial nucleus pressure, and yet both injuries cause that pressure to fall. Hence, either injury reduces the risk of the other, so the two disc degeneration "phenotypes" can be viewed as distinct (Adams and Dolan, 2012). Some discs, of course, exhibit features of both phenotypes, possibly because a particular injury has damaged the endplate and annulus at the same time. Injuries to the annulus mainly impair a motion segment's resistance to bending and torsion, whereas injuries to the endplate mainly impair resistance to compression, so repair strategies for the two types of injury must be quite different (Iatridis et al., 2013).

Severe Disc Degeneration: A Final Common Pathway

Nucleus decompression and high annulus stresses cause a degenerating disc to bulge "like a flat tyre" and to lose height, typically by 3% per year (Hassett et al., 2003), which is much faster than nondegenerated discs (Videman et al., 2008a). Disc degeneration can be recognized on MRI scans 4 yrs after an initial injury (Kerttula et al., 2000) and the 3% per year height loss suggests that the degeneration process may run its full course over 1–3 decades. Attempts at disc repair, as evidenced by increased cell signaling, enzyme activity, and increased matrix turnover (Antoniou et al., 1996; Sivan et al., 2006) are frustrated by low cell density. Increasing stress gradients within the degenerating annulus probably cause the structure to delaminate (Stefanakis et al., 2014), and ultimately to collapse. Up to 90% of compressive load bearing can then be transferred from the disc to the neural arch (Pollintine et al., 2004), with harmful consequences for the apophyseal joints (Robson-Brown et al., 2008). Disc narrowing also reduces tension in the annulus and intervertebral ligaments, thereby reducing the spine's resistance to bending, in the short term (Adams et al., 1987; Zhao et al., 2005). Stability is eventually restored by the growth of osteophytes around the vertebral body margin (Al-Rawahi et al., 2011) and in the apophyseal joints of the neural arch (Tischer et al., 2006). Extreme loss of disc height can obliterate the disc space, as the spine fuses.

TABLE 1. Disc Degeneration Increases with Age: Data from 600 Cadaveric Discs (Miller et al., 1988)

Age (yrs)	Grade 2	Grade 3	Grade 4
30–39	56	15	4
40–49	56	33	8
50–59	40	42	11
60–69	10	36	52
>70	7	49	42

The % of discs that had progressed to each grade of "degeneration" (scale 1–4) is shown. Grade 4 discs showed unambiguous (structural) degeneration, whereas Grade 2 discs showed age-related biochemical changes with minimal structural changes. Grade 3 discs showed a variable mixture of age-related changes and "isolated" structural changes. Young and healthy Grade 1 discs (not shown in the Table) caused values for each age-range to total 100%.

What Proportion of Old Discs Become Degenerated?

The most reliable data are probably from the meta-analysis of 600 cadaveric discs (Miller et al., 1988), which were graded for degeneration on a scale of 1–4, following dissection and direct visual observation. All Grade 4 discs showed unambiguous "structural" degeneration, and Grade 3 discs showed a mixture of age-related biochemical changes (see above), possibly with some "isolated" structural defects. As shown in Table 1, unambiguous (Grade 4) degeneration increased from 4% at age 30–39 yrs to 42% above age 70 yrs. Marginal (Grade 3) degeneration increased from 15 to 49% over the same age ranges. Male discs were more likely than female to show Grade 4 degeneration at an early age (<60 yrs) but there were only minor sex differences in older discs (Miller et al., 1988). Broadly, similar age-related trends have been reported in other cadaveric studies (Antoniou et al., 1996; Siemionow et al., 2011).

Imaging studies can reveal the prevalence of disc degeneration in large populations, although the nature of the "degeneration" is less certain than in cadavers. Magnetic resonance imaging (MRI; Cheung et al., 2009) and radiography (de Schepper et al., 2010) both show increasing prevalence with age, and at lower lumbar levels. Conventional MRI detects age-related water loss better than structural changes in the annulus and endplate (Videman et al., 2008b), and so naturally overestimates the incidence of true degeneration. Radiographs, in contrast, emphasize disc narrowing, and vertebral osteophytes, and have shown that the former feature is more common in men, and the latter in women (de Schepper et al., 2010).

WHY ARE SOME DEGENERATED DISCS PAINFUL?

Recent imaging studies on large populations have confirmed a strong statistical association between back pain and increasing intervertebral disc

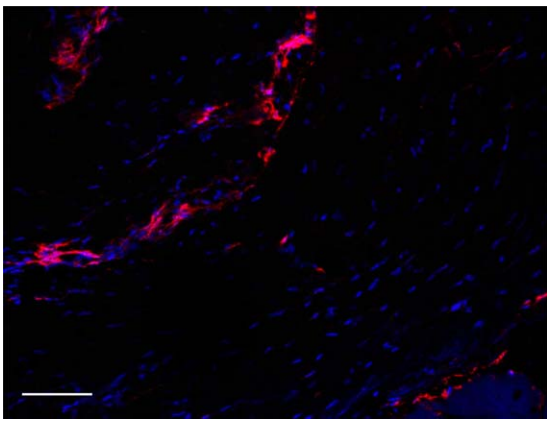

Fig. 8. Invading capillaries follow free surfaces, and splits between adjacent lamellae, in the annulus. In this 30 μm-thick frozen section of surgically removed herniated annulus fibrosus, immunofluorescence, and confocal microscopy have been used to demonstrate the presence of endothelial cells containing CD31 (stained red). Cell nuclei are counterstained blue using DAPI. The orientation of annulus lamellae is parallel to the elongated nuclei. (Bar = 100 μm). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

degeneration, although many individuals with severe disc degeneration report no back pain (Cheung et al., 2009; de Schepper et al., 2010). These variable links suggest that it is only certain features of disc degeneration that cause back pain. "Discogenic pain" is used here to refer to pain that arises directly from intervertebral disc tissue.

Invasion of Blood Vessels and Nerves

Structural damage to the endplate or outer annulus provides an opportunity for blood vessels and nerves to invade the disc. Annulus fissures exhibit low compressive stress (Stefanakis et al., 2012), so that blood vessels can grow within them without collapsing. In addition, fissures allow focal swelling, leading to a loss of proteoglycans, which normally inhibit blood vessels (Johnson et al., 2005) and nerves (Johnson et al., 2002). Ingrowing capillaries, and chondrocyte-like disc cells, can secrete neurotrophic factors, which then encourage nerve ingrowth (Freemont et al., 2002), especially in more degenerated discs (Purmessur et al., 2008). In this way, structural defects in a degenerating annulus are mechanically and chemically conducive to revascularization and reinnervation (Fig. 8), and are associated with discogenic pain (Videman and Nurminen, 2004; Peng et al., 2006). Similar arguments probably apply to the endplate, which has also been identified as a pain source (Peng et al., 2009). Endplate defects show evidence of extra-dense innervation (Fields et al., 2014), but endplate nerves are unlikely to grow into the adjacent disc unless there is a gross breach in the layer of hyaline cartilage, which normally prohibits ingrowth (Fig. 3). Nerves are reported to be more common in endplate defects than in annular tears (Fields et al., 2014), but this may be because both structures were sampled close to the mid-sagittal plane, and annulus tears commonly extend to the posterolateral margins of the disc.

Sensitization of Nerves: Inflammation and Infection

The severe and unremitting nature of much discogenic back pain and sciatica suggests that ingrowing nerves, and irritated nerve roots, can become oversensitized to mechanical stimuli, probably by inflammatory mechanisms (Burke et al., 2002; Shamji et al., 2010). Animal experiments have demonstrated that tumor necrosis factor alpha (TNFα) can sensitize nerves in this way, raising the hope that blocking this inflammatory agent may help to relieve pain in humans (Korhonen et al., 2006) as it does in animals (Olmarker et al., 2003). Sensitization may also arise from the presence of anaerobic bacteria, which infect the nucleus of some herniated discs (Albert et al., 2013a). This probably explains why antibiotic treatments have been shown recently to reduce discogenic back pain in certain patients (Albert et al., 2013b).

Provocation of Sensitized Nerves

A third likely factor in discogenic pain is the generation of stress concentrations within damaged and degenerated disc tissues (Adams et al., 2000a). Even if overall loading of a degenerated disc is normal, stress concentrations can still create high local strains (deformations) that could disturb sensitized nerves.

WHY DO SOME DISCS DEGENERATE MORE THAN OTHERS?

Discs Degenerate Because They Are Injured

As discussed above, physical damage to annulus or endplate creates abnormal stress distributions within a disc, which in turn lead to progressive structural collapse accompanied by abnormal disc cell biology. Tissue repair is frustrated by low cell density (Antoniou et al., 1996; Adams and Roughley, 2006), and any further physical disruption of disturbed tissue can provoke severe inflammation (Ulrich et al., 2007) involving "extrinsic" blood-borne cells. Lower lumbar discs are affected most because they are subjected to the highest mechanical stresses, including bending (Adams and Dolan, 1991). Similarly, the posterior annulus is affected more than the anterior because it is usually loaded more severely (Adams et al., 2000a). Animal models (Holm et al., 2004; Ulrich et al., 2007), and follow-up studies in humans (Kerttula et al., 2000; Carragee et al., 2009) confirm that injuries to annulus or endplate lead inexorably to disc degeneration.

Are Degenerated Discs Often "Injured"?

Some spine scientists resist the concept of disc injury. Other musculoskeletal tissues, including

tendons, menisci and vertebrae, are acknowledged to weaken with age (to an extent that depends on lifestyle, hormones and genetic inheritance) so that they can be damaged by everyday mechanical loading (Myers and Wilson, 1997; Wang, 2006; Snoeker et al., 2013). However, intervertebral discs are deemed only to "degenerate," or not. Resistance to the concept of disc injury may arise from the misconception that "injury" must be equated with "trauma," but this is not the case. Injury simply means that a structure has been physically disrupted, and this can happen either because it was extremely weak, or because it was loaded severely, or because it was loaded repetitively so that "fatigue" damage accumulated within it (Adams and Hutton, 1985). Even a sudden injury can occur in the absence of external violence, if internal muscle forces are very high, as they are during sudden or unexpected events (Mannion et al., 2000). As an extreme example, uncontrolled co-contraction of trunk muscles is known to cause vertebral fracture during epileptic fits (Vascancelos, 1973). There is ready acceptance that old and weak vertebrae can be injured during everyday activities such as trying to open a window (Myers and Wilson, 1997; Jiang et al., 2010) but this is because radiographs provide unambiguous evidence of the disrupted structure. Our appreciation of the role of injury in cartilage degeneration would be greatly enhanced if MRI was able to visualize cartilage damage as clearly as radiographs can identify a fractured or deformed bone.

The epidemiological evidence is consistent with an injury and fatigue "model" of disc degeneration. Degeneration (including prolapse) is associated with severe spinal loading (Videman et al., 1990; Schmitt et al., 2004) especially activities which involve forward bending (Kelsey et al., 1984; Seidler et al., 2003). More generally, back pain is related to sudden injuries and maximal efforts (Magora, 1973). But neither disc degeneration nor back pain are strongly related to moderately increased spinal loading arising from body weight (Videman et al., 2010), occupation (Videman et al., 2006), or leisure activities (Videman et al., 2007), presumably because all skeletal tissues eventually adapt to moderate and habitual levels of loading (Skrzypiec et al., 2007; Rumian et al., 2009; Sugiyama et al., 2012). Cyclic loading of animal tendons causes deterioration if the loading is severe, and adaptation if it is moderate. (Andarawis-Puri et al., 2012). In the words of Nietzsche: "What does not kill me makes me stronger!"

REFERENCES

Adams M, Bogduk N, Burton K, Dolan P. 2013. The Biomechanics of Back Pain. 3rd Ed. Edinburgh: Churchill Livingstone.

Adams MA, Dolan P. 1991. A technique for quantifying the bending moment acting on the lumbar spine in vivo. J Biomech 24:117–126.

Adams MA, Dolan P. 2012. Intervertebral disc degeneration: Evidence for two distinct phenotypes. J Anat 221:497–506.

Adams MA, Hutton WC. 1982. Prolapsed intervertebral disc. A hyperflexion injury 1981 Volvo Award in Basic Science. Spine 7: 184–191.

Adams MA, Hutton WC. 1985. Gradual disc prolapse. Spine 10:524–531.

Adams MA, Roughley PJ. 2006. What is intervertebral disc degeneration, and what causes it? Spine 31:2151–2161.

Adams MA, Dolan P, Hutton WC. 1986. The stages of disc degeneration as revealed by discograms. J Bone Joint Surg [Br] 68:36–41.

Adams MA, Dolan P, Hutton WC. 1987. Diurnal variations in the stresses on the lumbar spine. Spine 12:130–137.

Adams MA, McMillan DW, Green TP, Dolan P. 1996a. Sustained loading generates stress concentrations in lumbar intervertebral discs. Spine 21:434–438.

Adams MA, McNally DS, Dolan P. 1996b. 'Stress' distributions inside intervertebral discs. The effects of age and degeneration. J Bone Joint Surg Br 78:965–972.

Adams MA, Freeman BJ, Morrison HP, Nelson IW, Dolan P. 2000a. Mechanical initiation of intervertebral disc degeneration. Spine 25:1625–1636.

Adams MA, May S, Freeman BJ, Morrison HP, Dolan P. 2000b. Effects of backward bending on lumbar intervertebral discs. Relevance to physical therapy treatments for low back pain. Spine 25:431–437; discussion 438.

Adams MA, Dolan P, McNally DS. 2009. The internal mechanical functioning of intervertebral discs and articular cartilage, and its relevance to matrix biology. Matrix Biol 28:384–389.

Adams MA, Stefanakis M, Dolan P. 2010. Healing of a painful intervertebral disc should not be confused with reversing disc degeneration: Implications for physical therapies for discogenic back pain. Clin Biomech (Bristol, Avon) 25:961–971.

Al-Rawahi M, Luo J, Pollintine P, Dolan P, Adams MA. 2011. Mechanical function of vertebral body osteophytes, as revealed by experiments on cadaveric spines. Spine 36:770–777.

Albert HB, Lambert P, Rollason J, Sorensen JS, Worthington T, Pedersen MB, Norgaard HS, Vernallis A, Busch F, Manniche C, Elliott T. 2013a. Does nuclear tissue infected with bacteria following disc herniations lead to Modic changes in the adjacent vertebrae? Eur Spine J 22:690–696.

Albert HB, Sorensen JS, Christensen BS, Manniche C. 2013b. Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): A double-blind randomized clinical controlled trial of efficacy. Eur Spine J 22: 697–707.

Andarawis-Puri N, Sereysky JB, Sun HB, Jepsen KJ, Flatow EL. 2012. Molecular response of the patellar tendon to fatigue loading explained in the context of the initial induced damage and number of fatigue loading cycles. J Orthop Res 30:1327–1334.

Antoniou J, Steffen T, Nelson F, Winterbottom N, Hollander AP, Poole RA, Aebi M, Alini M. 1996. The human lumbar intervertebral disc: Evidence for changes in the biosynthesis and denaturation of the extracellular matrix with growth, maturation, ageing, and degeneration. J Clin Invest 98:996–1003.

Ayotte DC, Ito K, Tepic S. 2001. Direction-dependent resistance to flow in the endplate of the intervertebral disc: An ex vivo study. J Orthop Res 19:1073–1077.

Battie MC, Videman T. 2006. Lumbar disc degeneration: Epidemiology and genetics. J Bone Joint Surg Am 88 Suppl 2:3–9.

Battie MC, Videman T, Levalahti E, Gill K, Kaprio J. 2008. Genetic and environmental effects on disc degeneration by phenotype and spinal level: A multivariate twin study. Spine 33:2801–2808.

Benneker LM, Heini PF, Alini M, Anderson SE, Ito K. 2005. 2004 Young Investigator Award Winner: Vertebral endplate marrow contact channel occlusions and intervertebral disc degeneration. Spine 30:167–173.

Bibby SR, Jones DA, Ripley RM, Urban JP. 2005. Metabolism of the intervertebral disc: Effects of low levels of oxygen, glucose, and pH on rates of energy metabolism of bovine nucleus pulposus cells. Spine 30:487–496.

Brinckmann P, Frobin W, Hierholzer E, Horst M. 1983. Deformation of the vertebral end-plate under axial loading of the spine. Spine 8:851–856.

Burke JG, Watson RWG, McCormack D, Dowling FE, Walsh MG, Fitzpatrick JM. 2002. Intervertebral discs which cause low back pain secrete high levels of proinflammatory mediators. J Bone Joint Surg Br 84-B:196–201.

Carragee EJ, Don AS, Hurwitz EL, Cuellar JM, Carrino J, Herzog R. 2009. 2009 ISSLS Prize Winner: Does discography cause accelerated progression of degeneration changes in the lumbar disc: A ten-year matched cohort study. Spine 34:2338–2345.

Cheung KM, Karppinen J, Chan D, Ho DW, Song YQ, Sham P, Cheah KS, Leong JC, Luk KD. 2009. Prevalence and pattern of lumbar magnetic resonance imaging changes in a population study of one thousand forty-three individuals. Spine 34:934–940.

de Schepper EI, Damen J, van Meurs JB, Ginai AZ, Popham M, Hofman A, Koes BW, Bierma-Zeinstra SM. 2010. The association between lumbar disc degeneration and low back pain: The influence of age, gender, and individual radiographic features. Spine 35:531–536.

DeGroot J, Verzijl N, Wenting-Van Wijk MJ, Jacobs KM, Van El B, Van Roermund PM, Bank RA, Bijlsma JW, TeKoppele JM, Lafeber FP. 2004. Accumulation of advanced glycation end products as a molecular mechanism for aging as a risk factor in osteoarthritis. Arthritis Rheum 50:1207–1215.

Dolan P, Earley M, Adams MA. 1994. Bending and compressive stresses acting on the lumbar spine during lifting activities. J Biomech 27:1237–1248.

Dolan P, Luo J, Pollintine P, Landham PR, Stefanakis M, Adams MA. 2013. Intervertebral disc decompression following endplate damage: Implications for disc degeneration depend on spinal level and age. Spine 38:1473–1481.

Fields AJ, Liebenberg EC, Lotz JC. 2014. Innervation of pathologies in the lumbar vertebral end plate and intervertebral disc. Spine J 14:513–521.

Freemont AJ, Watkins A, Le Maitre C, Baird P, Jeziorska M, Knight MT, Ross ER, O'Brien JP, Hoyland JA. 2002. Nerve growth factor expression and innervation of the painful intervertebral disc. J Pathol 197:286–292.

Gunzburg R, Parkinson R, Moore R, Cantraine F, Hutton W, Vernon-Roberts B, Fraser R. 1992. A cadaveric study comparing discography, magnetic resonance imaging, histology, and mechanical behavior of the human lumbar disc. Spine 17:417–426.

Haefeli M, Kalberer F, Saegesser D, Nerlich AG, Boos N, Paesold G. 2006. The course of macroscopic degeneration in the human lumbar intervertebral disc. Spine 31:1522–1531.

Handa T, Ishihara H, Ohshima H, Osada R, Tsuji H, Obata K. 1997. Effects of hydrostatic pressure on matrix synthesis and matrix metalloproteinase production in the human lumbar intervertebral disc. Spine 22:1085–1091.

Hassett G, Hart DJ, Manek NJ, Doyle DV, Spector TD. 2003. Risk factors for progression of lumbar spine disc degeneration: The Chingford Study. Arthritis Rheum 48:3112–3117.

Hastreiter D, Ozuna RM, Spector M. 2001. Regional variations in certain cellular characteristics in human lumbar intervertebral discs, including the presence of alpha-smooth muscle actin. J Orthop Res 19:597–604.

Holm S, Holm AK, Ekstrom L, Karladani A, Hansson T. 2004. Experimental disc degeneration due to endplate injury. J Spinal Disord Tech 17:64–71.

Iatridis JC, Ap Gwynn I. 2004. Mechanisms for mechanical damage in the intervertebral disc annulus fibrosus. J Biomech 37:1165–1175.

Iatridis JC, Nicoll SB, Michalek AJ, Walter BA, Gupta MS. 2013. Role of biomechanics in intervertebral disc degeneration and regenerative therapies: What needs repairing in the disc and what are promising biomaterials for its repair? Spine J 13:243–262.

Ishihara H, McNally DS, Urban JP, Hall AC. 1996. Effects of hydrostatic pressure on matrix synthesis in different regions of the intervertebral disk. J Appl Physiol 80:839–846.

Jiang G, Luo J, Pollintine P, Dolan P, Adams MA, Eastell R. 2010. Vertebral fractures in the elderly may not always be "osteoporotic". Bone 47:111–116.

Johnson WE, Caterson B, Eisenstein SM, Hynds DL, Snow DM, Roberts S. 2002. Human intervertebral disc aggrecan inhibits nerve growth in vitro. Arthritis Rheum 46:2658–64.

Johnson WE, Caterson B, Eisenstein SM, Roberts S. 2005. Human intervertebral disc aggrecan inhibits endothelial cell adhesion and cell migration in vitro. Spine 30:1139–47.

Kelsey JL, Githens PB, White AAd, Holford TR, Walter SD, O'Connor T, Ostfeld AM, Weil U, Southwick WO, Calogero JA. 1984. An epidemiologic study of lifting and twisting on the job and risk for acute prolapsed lumbar intervertebral disc. J Orthop Res 2:61–66.

Kerttula LI, Serlo WS, Tervonen OA, Paakko EL, Vanharanta HV. 2000. Post-traumatic findings of the spine after earlier vertebral fracture in young patients: Clinical and MRI study. Spine 25: 1104–1108.

Korhonen T, Karppinen J, Paimela L, Malmivaara A, Lindgren KA, Bowman C, Hammond A, Kirkham B, Jarvinen S, Niinimaki J, Veeger N, Haapea M, Torkki M, Tervonen O, Seitsalo S, Hurri H. 2006. The treatment of disc herniation-induced sciatica with infliximab: One-year follow-up results of FIRST II, a randomized controlled trial. Spine 31:2759–2766.

Lama P, Le Maitre CL, Dolan P, Tarlton JF, Harding IJ, Adams MA. 2013. Do intervertebral discs degenerate before they herniate, or after? Bone Joint J 95-B:1127–1133.

Le Maitre CL, Freemont AJ, Hoyland JA. 2007. Accelerated cellular senescence in degenerate intervertebral discs: A possible role in the pathogenesis of intervertebral disc degeneration. Arthritis Res Ther 9:R45.

Liebscher T, Haefeli M, Wuertz K, Nerlich AG, Boos N. 2011. Age-related variation in cell density of human lumbar intervertebral disc. Spine 36:153–159.

Magora A. 1973. Investigation of the relation between low back pain and occupation. IV. Physical requirements: Bending, rotation, reaching and sudden maximal effort. Scand J Rehabil Med 5: 186–190.

Mannion AF, Adams MA, Dolan P. 2000. Sudden and unexpected loading generates high forces on the lumbar spine. Spine 25: 842–852.

Maroudas A, Stockwell RA, Nachemson A, Urban J. 1975. Factors involved in the nutrition of the human lumbar intervertebral disc: Cellularity and diffusion of glucose in vitro. J Anat 120:113–130.

Meller R, Schiborra F, Brandes G, Knobloch K, Tschernig T, Hankemeier S, Haasper C, Schmiedl A, Jagodzinski M, Krettek C, Willbold E. 2009. Postnatal maturation of tendon, cruciate ligament, meniscus and articular cartilage: A histological study in sheep. Ann Anat 191:575–585.

Miller JA, Schmatz C, Schultz AB. 1988. Lumbar disc degeneration: Correlation with age, sex, and spine level in 600 autopsy specimens. Spine 13:173–178.

Moon SM, Yoder JH, Wright AC, Smith LJ, Vresilovic EJ, Elliott DM. In press. Evaluation of intervertebral disc cartilaginous endplate structure using magnetic resonance imaging. Eur Spine J 22: 1820–1828.

Myers ER, Wilson SE. 1997. Biomechanics of osteoporosis and vertebral fracture. Spine 22:25S–31S.

Olmarker K, Nutu M, Storkson R. 2003. Changes in spontaneous behavior in rats exposed to experimental disc herniation are blocked by selective TNF-alpha inhibition. Spine 28:1635–1641; discussion 1642.

Osti OL, Vernon-Roberts B, Fraser RD. 1990. 1990 Volvo Award in experimental studies. Anulus tears and intervertebral disc degeneration. An experimental study using an animal model. Spine 15: 762–767.

Palmgren T, Gronblad M, Virri J, Kaapa E, Karaharju E. 1999. An immunohistochemical study of nerve structures in the anulus fibrosus of human normal lumbar intervertebral discs. Spine 24: 2075–2079.

Peng B, Hao J, Hou S, Wu W, Jiang D, Fu X, Yang Y. 2006. Possible pathogenesis of painful intervertebral disc degeneration. Spine 31:560–566.

Peng B, Chen J, Kuang Z, Li D, Pang X, Zhang X. 2009. Diagnosis and surgical treatment of back pain originating from endplate. Eur Spine J 18:1035–1040.

Pollintine P, Przybyla AS, Dolan P, Adams MA. 2004. Neural arch load-bearing in old and degenerated spines. J Biomech 37:197–204.

Pollintine P, Luo J, Offa-Jones B, Dolan P, Adams MA. 2009. Bone creep can cause progressive vertebral deformity. Bone 45:466–472.

Przybyla A, Pollintine P, Bedzinski R, Adams MA. 2006. Outer annulus tears have less effect than endplate fracture on stress distributions inside intervertebral discs: Relevance to disc degeneration. Clin Biomech 21:1013–1019.

Purmessur D, Freemont AJ, Hoyland JA. 2008. Expression and regulation of neurotrophins in the nondegenerate and degenerate human intervertebral disc. Arthritis Res Therapy 10:R99.

Rajasekaran S, Bajaj N, Tubaki V, Kanna RM, Shetty AP. 2013. ISSLS prize winner: The anatomy of failure in lumbar disc herniation: An in vivo, multimodal, prospective study of 181 subjects. Spine 38:1491–1500.

Robson-Brown K, Pollintine P, Adams MA. 2008. Biomechanical implications of degenerative joint disease in the apophyseal joints of human thoracic and lumbar vertebrae. Am J Phys Anthropol 136:318–326.

Rodriguez AG, Slichter CK, Acosta FL, Rodriguez-Soto AE, Burghardt AJ, Majumdar S, Lotz JC. 2011. Human disc nucleus properties and vertebral endplate permeability. Spine 36:512–520.

Rodriguez AG, Rodriguez-Soto AE, Burghardt AJ, Berven S, Majumdar S, Lotz JC. 2012. Morphology of the human vertebral endplate. J Orthop Res 30:280–287.

Rumian AP, Draper ER, Wallace AL, Goodship AE. 2009. The influence of the mechanical environment on remodelling of the patellar tendon. J Bone Joint Surg Br 91:557–564.

Schmitt H, Dubljanin E, Schneider S, Schiltenwolf M. 2004. Radiographic changes in the lumbar spine in former elite athletes. Spine 29:2554–2559.

Schollum ML, Robertson PA, Broom ND. 2008. ISSLS prize winner: Microstructure and mechanical disruption of the lumbar disc annulus: Part I: A microscopic investigation of the translamellar bridging network. Spine 33:2702–2710.

Schollum ML, Robertson PA, Broom ND. 2009. A microstructural investigation of intervertebral disc lamellar connectivity: Detailed analysis of the translamellar bridges. J Anat 214:805–816.

Seidler A, Bolm-Audorff U, Siol T, Henkel N, Fuchs C, Schug H, Leheta F, Marquardt G, Schmitt E, Ulrich PT, Beck W, Missalla A, Elsner G. 2003. Occupational risk factors for symptomatic lumbar disc herniation: A case-control study. Occup Environ Med 60: 821–830.

Shamji MF, Setton LA, Jarvis W, So S, Chen J, Jing L, Bullock R, Isaacs RE, Brown C, Richardson WJ. 2010. Proinflammatory cytokine expression profile in degenerated and herniated human intervertebral disc tissues. Arthritis Rheum 62:1974–1982.

Siemionow K, An H, Masuda K, Andersson G, Cs-Szabo G. 2011. The effects of age, sex, ethnicity, and spinal level on the rate of intervertebral disc degeneration: A review of 1712 intervertebral discs. Spine 36:1333–1339.

Sivan SS, Tsitron E, Wachtel E, Roughley PJ, Sakkee N, van der Ham F, DeGroot J, Roberts S, Maroudas A. 2006. Aggrecan turnover in human intervertebral disc as determined by the racemization of aspartic acid. J Biol Chem 281:13009–13014.

Sivan SS, Wachtel E, Tsitron E, Sakkee N, van der Ham F, Degroot J, Roberts S, Maroudas A. 2008. Collagen turnover in normal and degenerate human intervertebral discs as determined by the racemization of aspartic acid. J Biol Chem 283:8796–8801.

Skrzypiec D, Tarala M, Pollintine P, Dolan P, Adams MA. 2007. When are intervertebral discs stronger than their adjacent vertebrae? Spine 32:2455–2461.

Snoeker BA, Bakker EW, Kegel CA, Lucas C. 2013. Risk factors for meniscal tears: A systematic review including meta-analysis. J Orthop Sports Phys Ther 43:352–367.

Stefanakis M, Al-Abbasi M, Harding I, Pollintine P, Dolan P, Tarlton J, Adams MA. 2012. Annulus fissures are mechanically and chemically conducive to the ingrowth of nerves and blood vessels. Spine 37:1883–1891.

Stefanakis M, Luo J, Pollintine P, Dolan P, Adams MA. 2014 (in press). ISSLS prize winner: Mechanical influences in progressive intervertebral disc degeneration. Spine.

Sugiyama T, Meakin LB, Browne WJ, Galea GL, Price JS, Lanyon LE. 2012. Bones' adaptive response to mechanical loading is essentially linear between the low strains associated with disuse and the high strains associated with the lamellar/woven bone transition. J Bone Miner Res 27:1784–1793.

Temple MM, Bae WC, Chen MQ, Lotz M, Amiel D, Coutts RD, Sah RL. 2007. Age- and site-associated biomechanical weakening of human articular cartilage of the femoral condyle. Osteoarthritis Cartilage 15:1042–1052.

Thompson JP, Pearce RH, Schechter MT, Adams ME, Tsang IK, Bishop PB. 1990. Preliminary evaluation of a scheme for grading the gross morphology of the human intervertebral disc. Spine 15:411–415.

Tischer T, Aktas T, Milz S, Putz RV. 2006. Detailed pathological changes of human lumbar facet joints L1-L5 in elderly individuals. Eur Spine J 15:308–315.

Ulrich JA, Liebenberg EC, Thuillier DU, Lotz JC. 2007. ISSLS prize winner: Repeated disc injury causes persistent inflammation. Spine 32:2812–2819.

Vascancelos D. 1973. Compression fractures of the vertebra during major epileptic seizures. Epilepsia 14:323–328.

Videman T, Nurminen M. 2004. The occurrence of anular tears and their relation to lifetime back pain history: A cadaveric study using barium sulfate discography. Spine 29:2668–2676.

Videman T, Nurminen M, Troup JD. 1990. 1990 Volvo Award in clinical sciences. Lumbar spinal pathology in cadaveric material in relation to history of back pain, occupation, and physical loading. Spine 15:728–740.

Videman T, Battie MC, Ripatti S, Gill K, Manninen H, Kaprio J. 2006. Determinants of the progression in lumbar degeneration: A 5-year follow-up study of adult male monozygotic twins. Spine 31: 671–678.

Videman T, Levalahti E, Battie MC. 2007. The effects of anthropometrics, lifting strength, and physical activities in disc degeneration. Spine 32:1406–1413.

Videman T, Battie MC, Parent E, Gibbons LE, Vainio P, Kaprio J. 2008a. Progression and determinants of quantitative magnetic resonance imaging measures of lumbar disc degeneration: A five-year follow-up of adult male monozygotic twins. Spine 33: 1484–1490.

Videman T, Gibbons LE, Battie MC. 2008b. Age- and pathology-specific measures of disc degeneration. Spine 33:2781–2788.

Videman T, Gibbons LE, Kaprio J, Battie MC. 2010. Challenging the cumulative injury model: Positive effects of greater body mass on disc degeneration. Spine J 10:26–31.

Wade KR, Robertson PA, Broom ND. 2012. On how nucleus-endplate integration is achieved at the fibrillar level in the ovine lumbar disc. J Anat 221:39–46.

Walter BA, Korecki CL, Purmessur D, Roughley PJ, Michalek AJ, Iatridis JC. 2011. Complex loading affects intervertebral disc mechanics and biology. Osteoarthritis Cartilage 19:1011–1018.

Wang JH. 2006. Mechanobiology of tendon. J Biomech 39:1563–1582.

Weiler C, Nerlich AG, Zipperer J, Bachmeier BE, Boos N. 2002. 2002 SSE Award competition in basic science: Expression of major matrix metalloproteinases is associated with intervertebral disc degradation and resorption. Eur Spine J 11:308–320.

Zhao F, Pollintine P, Hole BD, Dolan P, Adams MA. 2005. Discogenic origins of spinal instability. Spine 30:2621–2630.