

Healing of a painful intervertebral disc should not be confused with reversing disc degeneration: Implications for physical therapies for discogenic back pain

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ABSTRACT

Background: Much is known about intervertebral disc degeneration, but little effort has been made to relate this information to the clinical problem of discogenic back pain, and how it might be treated.

Methods: We re-interpret the scientific literature in order to provide a rationale for physical therapy treatments for discogenic back pain.

Interpretation: Intervertebral discs deteriorate over many years, from the nucleus outwards, to an extent that is influenced by genetic inheritance and metabolite transport. Age-related deterioration can be accelerated by physical disruption, which leads to disc “degeneration” or prolapse. Degeneration most often affects the lower lumbar discs, which are loaded most severely, and it is often painful because nerves in the peripheral annulus or vertebral endplate can be sensitised by inflammatory-like changes arising from contact with blood or displaced nucleus pulposus. Surgically-removed human discs show an active inflammatory process proceeding from the outside-in, and animal studies confirm that effective healing occurs only in the outer annulus and endplate, where cell density and metabolite transport are greatest. Healing of the disc periphery has the potential to relieve discogenic pain, by re-establishing a physical barrier between nucleus pulposus and nerves, and reducing inflammation.

Conclusion: Physical therapies should aim to promote healing in the disc periphery, by stimulating cells, boosting metabolite transport, and preventing adhesions and re-injury. Such an approach has the potential to accelerate pain relief in the disc periphery, even if it fails to reverse age-related degenerative changes in the nucleus.

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1. Introduction

Intervertebral discs (Fig. 1) are a common source of severe back pain and sciatica (Kuslich et al., 1991; Cheung et al., 2009) but not all of the pathological changes seen in old discs are likely to cause pain (Boos et al., 1995; Jensen et al., 1994; Videman et al., 2003). Biochemical ageing mostly affects the aneural nucleus and inner anulus (Antoniou et al., 1996a) and gives rise to a “dark disc” on MRI. Age-related changes occur from the inside out (Haefeli et al., 2006), progress over many years (Hassett et al., 2003) and are difficult to modify because central regions of the disc have an extremely low cell density. Pain on the other hand is associated with discrete structural changes in the peripheral anulus (Moneta et al., 1994; Videman and Nurminen, 2004; Freemont et al., 1997; Peng et al., 2009a) and vertebral endplate (Freemont et al., 2002; Peng et al., 2009b), and the consequent reduction in disc height (Cheung et al., 2009; de Schepper et al., 2010). Peripheral regions of the disc are innervated (Fagan et al., 2003), have a relatively high cell density (Hastreiter et al., 2001) and nutrient supply (Ferguson et al., 2004), and can heal effectively from the outside-in (Osti et al., 1990), at least in young animals.

The purpose of the present review is to distinguish as clearly as possible between old and painful discs, and to suggest which features of ageing discs should be viewed as “disc degeneration”. These distinctions lead on to the proposal that interventions for discogenic back pain should attempt to promote healing in the disc periphery, rather than halt or reverse age-related changes in the disc nucleus. The efficacy of any intervention for back pain depends on the accurate

identification of patients who are most likely to benefit, so the review ends with a few suggestions to aid patient selection.

2. Disc growth and ageing

The healing potential of an intervertebral disc depends on its cell population and metabolite transport, and both of these factors change with increasing age. In the new-born disc, blood vessels from the vertebral bodies and the disc periphery penetrate to most regions of the anulus, but not the nucleus (Hassler, 1969). Following weight-bearing, these blood vessels retreat from the disc, so that by the age of 5 years, only its periphery is vascularised (Fig. 2). Growth increases metabolite transport difficulties within the largely-avascular disc, and probably explains why cell density decreases throughout the growth period (Liebscher et al., in press; Boos et al., 2002). The disc's healing ability is further reduced in late childhood by loss of the large and metabolically-active notochordal cells from the nucleus pulposus, leaving only smaller and less active chondrocyte-like cells (Guehring et al., 2008).

Ageing beyond skeletal maturity reduces the proteoglycan content of the nucleus (Roughley, 2004), and because proteoglycans are required to attract water, their loss causes the nucleus to become less hydrated (Antoniou et al., 1996a) and fluid pressure within it falls (Adams et al., 1996). As a result, the disc bulges radially (Brinckmann and Horst, 1985; Heuer et al., 2007). After 40 years of age, there is an increased vascular invasion of the disc periphery, mostly from the outer anulus but also from the endplate (Yasuma et al., 1993; Repanti et al., 1998). This may be caused by the appearance of structural defects, or by the loss of proteoglycans which normally inhibit capillary growth (Johnson et al., 2005). Other biochemical changes in old discs include increased deposition of coarse fibres of collagen Type I in the inner anulus and nucleus (Schollmeier et al., 2000) and increased cross-linking of disc collagens (Pokharna and Phillips, 1998). Further collagen cross-linking with tissue sugars (non-enzymatic glycation) makes cartilaginous tissues stiffer and more easily injured, and gives them a brown discoloration (DeGroot et al., 2004) (Fig. 3). A disc's healing potential may decline with age, even if

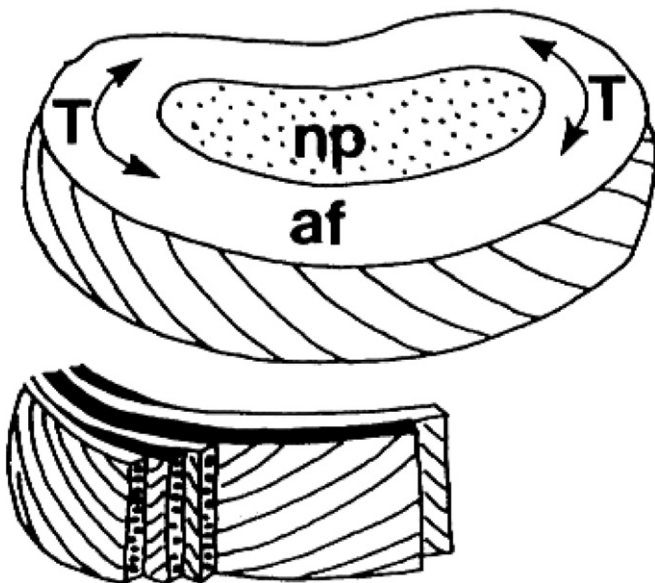


Fig. 1. (Upper) Intervertebral discs have a soft central nucleus pulposus (np) surrounded by the lamellae of the anulus fibrosus (af). The nucleus normally behaves as a fluid, and so compressive loading of the spine generates a hydrostatic pressure in the nucleus, and tensile forces (T) in the anulus. (Lower) Collagen fibres in the anulus are orientated differently in adjacent lamellae.

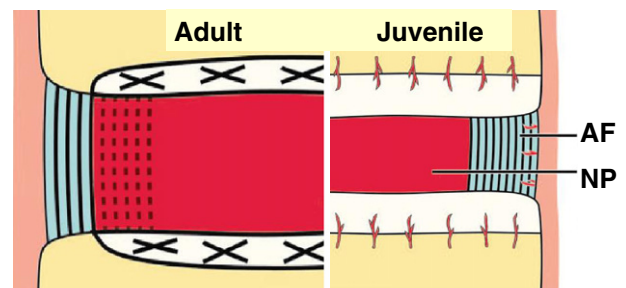


Fig. 2. Composite diagram showing an adult (left) and juvenile (right) disc in the mid-sagittal plane. The juvenile disc has a blood supply that penetrates the outer few mm of anulus, and also the cartilage endplate. This peripheral vasculature is normally lost in the adult, as the inner annulus becomes more fibrous, and the cartilage endplate becomes less permeable as marrow cavities linking it to the subchondral bone become blocked. Adapted from Roughley(24) with permission.

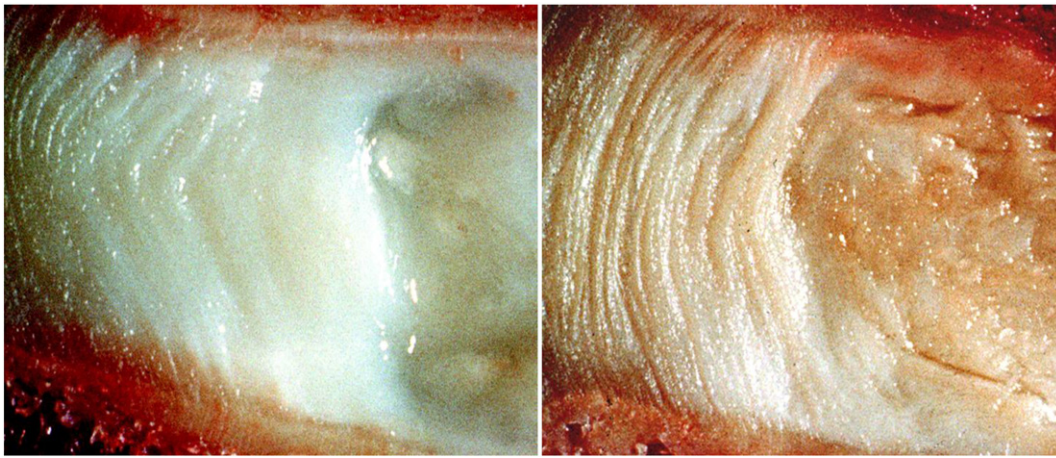


Fig. 3. Mid-sagittal sections of intervertebral discs showing the biochemical appearance of aging. Left: disc typical of ages 20–30 years. Right: disc typical of ages 50–60 years. Only the anterior half of each disc is shown. Note that ageing makes the nucleus and inner annulus more fibrous, and the whole disc becomes brown as a result of non-enzymatic glycation.

apparent cell density is maintained (Vernon-Roberts et al., 2008), because of increasing cell senescence (Roberts et al., 2006) and apoptosis (Zhang et al., 2008) and because it becomes more difficult for cells to turn-over (repair) the increasingly cross-linked matrix.

Old discs function more-or-less normally, although the fluid-like nucleus is decreased in extent, and more compressive load-bearing is resisted by the annulus (Adams et al., 1996), causing it to bulge outwards and lose height. These physical changes create some slack in the fibres of the outer annulus, so that it resists bending less (Zhao et al., 2005). Contrary to popular belief, a dehydrated nucleus is less likely than a hydrated nucleus to herniate through the annulus in response to severe mechanical loading (Adams et al., 1987).

3. Disc degeneration

More severe changes can affect certain discs, particularly those in the lower lumbar spine. Their structure becomes disrupted, in the form of radial and circumferential tears in the annulus, inward collapse of annulus lamellae, and disruption of the endplate. These structural changes have a dramatic influence on disc function (Fig. 4), causing gross decompression of the nucleus (Adams et al., 1996), high stress concentrations in the annulus (Adams et al., 1996), reduced stability (Zhao et al., 2005) and increased load-bearing by the neural arch (Pollintine et al., 2004). As argued in detail elsewhere, it is these structural changes that merit the description “disc degeneration” (Adams and Roughley, 2006). Age-related changes in composition (Fig. 3) constitute a major risk factor for disc degeneration because they weaken the matrix and concentrate stress within it, although (as noted above) they do not predispose a disc to prolapse.

All of the structural features of human disc degeneration (Fig. 5) can be initiated by mechanical loading. Laboratory experiments on cadaveric spines have shown that endplates can be damaged by high or repetitive compressive loading (Brinckmann et al., 1988; Brinckmann et al., 1989) causing the nucleus to become decompressed (Adams et al., 2000a) and allowing the annulus to bulge inwards (Adams et al., 2000a) and outwards (Brinckmann and Horst, 1985). Complex loading in bending and compression can cause a disc to prolapse, either as an injury (Adams et al., 2000a), or as a result of gradual radial fissure growth from inner to outer annulus (Adams and Hutton, 1985). Experiments on young animal spines *in vitro* support these cadaveric results (Tampier et al., 2007) and show how pressurised nucleus material can force its way through the annulus (Pezowicz et al., 2006). Detailed mechanisms have been further explained by mathematical models (Schmidt et al., 2007). Abnormal matrix stresses generated within injured discs (Adams et al., 2000a) (Fig. 4) reduce cell viability in the nucleus and initiate cell-mediated

degenerative changes (Haschtmann et al., 2008) so that disc composition becomes abnormal (Iatridis et al., 2007). These processes are slow, with degenerative changes becoming apparent only after several weeks or months, in young animals (Osti et al., 1990; Holm et al., 2004) or after several years, in human teenagers (Kerttula et al., 2000). Degenerated adult human discs lose 1–3% of their height per year (Hassett et al., 2003; Videman et al., 2008) with radial bulging

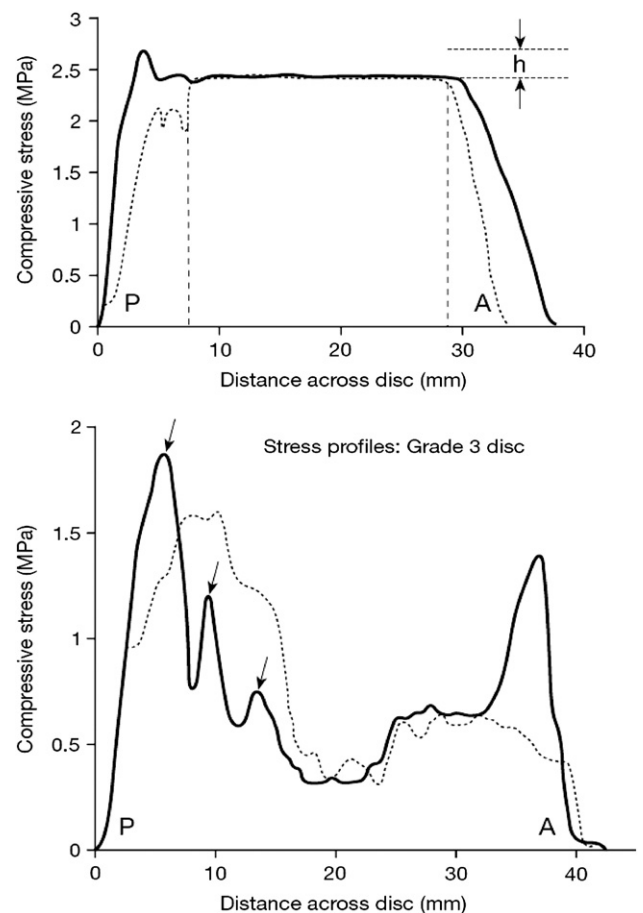


Fig. 4. Typical distributions of compressive stress across the mid-sagittal diameter of a healthy middle-aged lumbar disc (upper) and a young degenerated disc (lower). Stress concentrations (h) become very large with degeneration. P, A – posterior, anterior. Solid/dotted lines represent vertical/horizontal stress. Reproduced from Adams et al. (Adams et al., 2006) with permission.

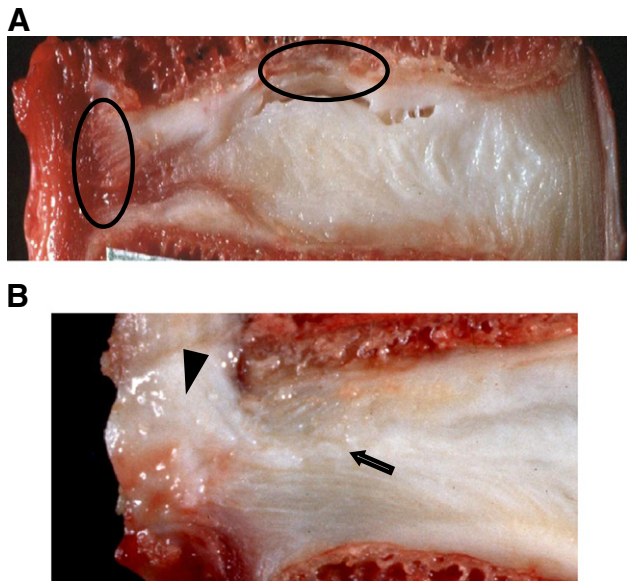


Fig. 5. Mid-sagittal sections of two cadaveric middle-aged intervertebral discs, posterior on left. (Upper) This disc has a (pre-existing) complete radial fissure from the nucleus to the posterior margin, and a deformed upper endplate. Areas that are likely to be painful, and capable of healing, are circled. (Lower) This disc was induced to prolapse in vitro by mechanical loading. The extruded mass of nucleus (solid arrow head) was expelled down a complete radial fissure (arrow). Adapted from Adams et al. (Adams et al., 2006) with permission.

increasing by 2% per year (Videman et al., 2008). The discs of laboratory animals age, degenerate and heal much faster than adult human discs because their smaller size and higher cell density make them more metabolically active (Lotz, 2004). All of this evidence suggests that reversing disc degeneration in adult humans would be a very slow process, if indeed it could be achieved at all (Kobayashi et al., 2008).

Genetic influences are important in disc ageing and degeneration, but their influence should not be exaggerated. Recent twin studies show that the heritability of disc degeneration is 29–54%, with the complementary environmental influences (46–71%) varying with spinal level (Battie et al., 2008). Earlier (higher) estimates of heritability referred to middle-aged women, and neglected the influence of spinal level (Sambrook et al., 1999). Most of the known genetic risks involve structural molecules such as collagens and proteoglycans (Battie et al., 2004) so they may exert their influence by weakening the extracellular matrix. Environmental influences explain why disc degeneration is generally worse in people with physically-demanding occupations (Videman et al., 2007). Not all mechanical loading is bad for discs however: only the most severe occupations and sporting activities appear to increase degeneration (Videman et al., 1995) whereas modest or gradual increases in disc loading may even have some beneficial effect (Videman et al., 2007; Adams and Dolan, 1997). The outer annulus, in particular, is able to adapt its strength to mechanical demands (Skrzypiec et al., 2007) probably because it has the highest cell density (Hastreiter et al., 2001) and is close to the peripheral blood supply.

4. Discogenic pain

4.1. Innervation of intervertebral discs

Lumbar discs are innervated posteriorly by the mixed sinuvertebral nerve, and anteriorly and laterally by fibres from the sympathetic chain (Bogduk et al., 1981). Sensory fibres of the sinuvertebral nerve normally reside only in the peripheral annulus and posterior longitudinal ligament (Bogduk et al., 1981; Coppes et al., 1997;

Palmgren et al., 1999). Some of these fibres contain neuropeptides such as Substance P (Coppes et al., 1997; Palmgren et al., 1999) or calcitonin gene-related peptide (CGRP) which are associated with nociception (Lawson et al., 1997; Ozawa et al., 2006). The highest concentration of sensory nerves (in sheep discs) lies in the peripheral annulus and central region of the endplate (Fagan et al., 2003) reflecting the blood supply. In degenerated and painful discs, sensory nerve fibres have been reported to grow into the annulus, both anteriorly (Freemont et al., 1997) and posteriorly (Peng et al., 2005). Nerve fibres have been reported in the nucleus (Freemont et al., 2002; Coppes et al., 1997), presumably by penetrating the vertebral endplates (Freemont et al., 2002; Fagan et al., 2003). Blood vessels show a similar distribution to nerves (Nerlich et al., 2007) and probably encourage the latter by secreting Nerve Growth Factor (Freemont et al., 2002). Ingrowth of nerves and blood vessels appears to be facilitated by the presence of a radial fissure (Peng et al., 2006a) by loss of nucleus pressure (Adams et al., 1996) which otherwise would collapse hollow blood vessels, and by loss of proteoglycans (Johnson et al., 2005; Johnson et al., 2002) particularly in the vicinity of annulus fissures (Fig. 6).

4.2. Disc degeneration and back pain

Recent large population studies provide conclusive evidence that disc degeneration is strongly associated with back pain, and in a dose-related manner (Cheung et al., 2009; de Schepper et al., 2010). However, degenerated discs are often observed in individuals without back pain, and relatively small studies tend to show variable associations between degeneration and pain, depending on how each is defined. For example, measures of disc 'degeneration' that reflect nucleus dehydration (or consequent annulus 'bulging') are often found in pain-free subjects (Jensen et al., 1994; Videman et al., 2003; Boden et al., 1990), whereas structural defects such as disc extrusions (Boos et al., 1995; Jensen et al., 1994) complete radial fissures (Videman and Nurminen, 2004; Peng et al., 2006a), endplate defects (Peng et al., 2009b; Hamanishi et al., 1994) and loss of annulus height (Videman et al., 2003; de Schepper et al., 2010) are more likely to be associated with pain. If all trivial or transient symptoms are included

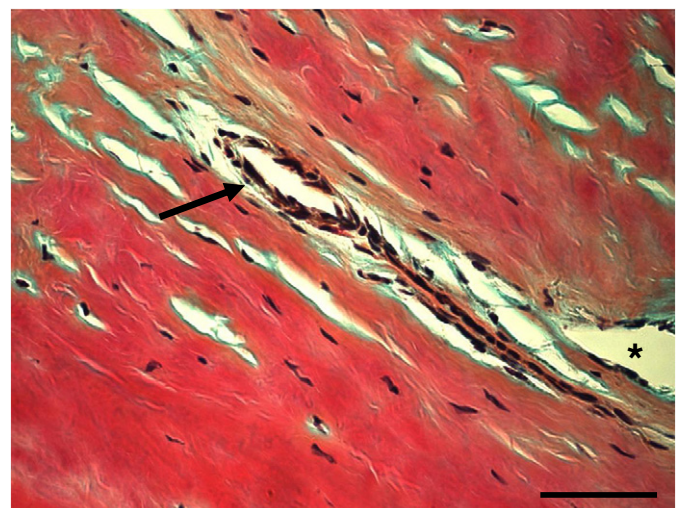


Fig. 6. Histological section in the transverse plane of the outer annulus fibrosus of a disrupted middle-aged disc. A blood vessel (arrow) has grown into a posterolateral radial fissure (*) close to the disc periphery at top left. Note the proliferation of cells around the fissure. The green margins of the numerous annulus tears suggest focal loss of proteoglycans (red) exposing the collagen (green). Proteoglycan loss around the margins of fissures could stimulate blood vessels to grow into them. (L2 disc, wax embedded, 7 μ m section, Masson's Trichrome stain, bar = 50 μ m, posterior on top).

as “back pain”, then it is difficult to find strong risk factors for the condition (Croft et al., 1999) doubtless because so many people have it that it has little discriminatory power. In the following discussion, we will consider only “severe” back pain, with the term being used to include symptoms that are disabling or long-lasting, or associated with physician consultations or work loss. The prevalence of such back pain arising from the disc is indicated by a study which found that 39% of patients had their pain reproduced by provocation discography (Schwarzer et al., 1995).

4.3. Localisation of discogenic pain

Many candidates for back surgery can have their back pain reproduced by mechanical stimulation of the outer posterior annulus and posterior longitudinal ligament (Kuslich et al., 1991). Provocation discography has been used to confirm that severe back pain in some patients is associated with defects in the vertebral endplate (Peng et al., 2009b) or with radial fissures in the annulus (Peng et al., 2005). Similarly, discogenic pain has been directly associated with concentrations of compressive stress measured in the posterolateral annulus (McNally et al., 1996). A cadaveric study has shown that the presence of a complete (‘leaking’) radial fissure (Fig. 5) quadruples the risk of having a medical history involving severe back pain, compared to having discs with fissures that affect only the inner annulus (Videman and Nurminen, 2004). A fissure extending into the outer annulus, but not leaking, only doubles this risk. (Annular tears identified on MRI scans are less well defined, and are not closely related to back pain (Cheung et al., 2009).) Large imaging studies have shown that endplate defects identified on MRI scans carry only a modest increased risk of severe back pain, and often are asymptomatic (Cheung et al., 2009; Hamanishi et al., 1994). Endplates may be less involved in back pain because blood vessels are more likely to grow into annulus defects than into endplate defects (Hassler, 1969).

4.4. Pain sensitisation

Pain provocation studies not only identify the disc periphery as a major pain source, they also show that only modest mechanical stimulation of these tissues is required to reproduce the patients’ typical pain. The concept of chemical ‘pain sensitisation’ (mechanical allodynia) in the spine has been well established by Olmarker and colleagues who showed in animal experiments that degenerated nucleus pulposus can cause morphological and functional changes in adjacent nerve roots (Kayama et al., 1996). These changes act synergistically with mechanical pressure to cause sciatica (Olmarker et al., 1998). (Strictly speaking, they alter the animals’ behaviour in a manner that suggests sciatica.) Pain sensitisation may explain sciatica in patients without radiological findings of gross disc herniation, and also why back pain progresses rapidly to sciatica in some patients. Proximity to nucleus pulposus increases mechanical sensitivity of nerve cells (Chen et al., 2004), possibly because of an inflammatory-like reaction involving tumor necrosis factor α (Goupille et al., 2007) which is secreted by nucleus cells. Recently, these animal studies have been extended to suggest that displaced nucleus pulposus can elicit back pain from nerves in the peripheral annulus (Olmarker, 2008) although back pain is difficult to detect in dumb animals. It appears therefore that a radial fissure in a disc can lead to chemical sensitisation and increased stresses (Fig. 4) in the innervated peripheral annulus, which then becomes a potent source of back pain. Pain sensitisation could also occur in the posterior annulus or longitudinal ligament as a result of inflammation driven by cells from disrupted blood vessels.

Similar events probably occur in the vertebral endplates, because severe back pain is associated with endplate damage (Peng et al., 2009b; Hamanishi et al., 1994) increased sensory innervation of the endplate (Freemont et al., 2002; Brown et al., 1997) and inflammatory

(“Modic”) changes in the vertebrae adjacent to the endplates (Albert and Manniche, 2007; Kuusma et al., 2007). However, pain sensitisation is probably more important in the outer annulus, because this is where compressive stress is concentrated in degenerated discs (Fig. 4), and where high tensile stresses are found near the “crack tip” of radial fissures (Pezowicz et al., 2006). On the other hand, pain sensitisation in the nucleus and central endplate may not be clinically significant if the nucleus is severely decompressed, as it often is in degenerated discs (Fig. 4). Also, the proteoglycan-rich hyaline cartilage endplate provides a more formidable barrier for nerves and blood vessels compared to the collagenous outer annulus.

The concept of pain sensitisation is strengthened by the recent finding that intradiscal injection of methylene blue can dramatically reduce discogenic back pain, for at least 2 years (Peng et al., 2010). Such a simple treatment could have no long-lasting mechanical effect, or reverse disc degeneration, although it could conceivably desensitise (or kill) nerve axons within the disc.

5. Disc healing in patients

Herniated disc tissue swells rapidly in tissue fluid, losing much of its proteoglycan content (Dolan et al., 1987) and this may explain why it is invaded by blood vessels and inflammatory cells (Repanti et al., 1998; Kobayashi et al., 2009). Levels of neovascularisation and inflammatory mediators are greater in extruded and sequestered disc tissue compared to protruded (“contained”) tissue (Yasuma et al., 1993; Nygaard et al., 1997), suggesting that an intact outer annulus is an effective barrier to inflammatory changes progressing inwards from the disc periphery.

Tissue removed from patients with discogenic back pain shows many biological changes, but it is difficult to distinguish between disc degeneration and healing, or to discern cause from effect. Nerves and blood vessels grow inwards in disrupted and painful discs (Freemont et al., 1997; Coppes et al., 1997), and annulus fissures often contain innervated granulation tissue (Peng et al., 2005; Peng et al., 2006a) and exhibit increased enzyme activity (Weiler et al., 2002).

6. Experimental disc healing

6.1. Gross responses to disc injury

These have been studied in mice (Lotz et al., 1998), rats (Ulrich et al., 2007; Iatridis et al., 1999), rabbits (Lipson and Muir, 1981), sheep (Osti et al., 1990), goats (Hoogendoorn et al., 2008) and pigs (Holm et al., 2004; Omlor et al., 2009). Interventions include lacerations or stab wounds to the annulus (Osti et al., 1990), endplate damage (Holm et al., 2004), enzymatic dissolution of the nucleus (Hoogendoorn et al., 2008) partial nucleotomy (Omlor et al., 2009), induced cell senescence (Zhou et al., 2007) and increased loading without damage (Iatridis et al., 1999). Responses typically include disorganization of the annulus fibrosus, and disc narrowing. Most of these experiments focus on degenerative changes in the disc that occur after injury, and more attention is given to the progressive deterioration of the inner annulus and nucleus than to healing of the outer annulus and endplate.

6.2. Healing of the annulus

Some healing is reported to occur in most young animals. Needle puncture in rabbit discs induced scar tissue around the margins of the lesion, with the scar becoming innervated by 4 weeks (Aoki et al., 2006). Nerve fibre formation was greater with a 5 mm-deep puncture (with nucleus herniation) compared to a 1 mm-deep puncture without herniation (Aoki et al., 2006). A 3 × 5 mm stab wound in the annulus of dog discs induced scar tissue, with mature fibroblasts and flat mesothelial cells around the wound margin (Hampton et al., 1989). A peripheral stab wound in sheep discs caused granulation

tissue to spread from the periphery into the injury site, creating new capillaries and encouraging nerve ingrowth (Osti et al., 1990). After several months, scar tissue in the outer 2–3 mm of anulus began to mature into a tissue with a dense regular collagen network, and some collagenous remodelling was apparent (Melrose et al., 2008). The inner anulus did not heal like this: in fact the original lesion progressed in towards the nucleus (Osti et al., 1990). Later experiments on sheep confirmed that mechanically-competent disc healing was confined to the outer few mm of anulus (Moore et al., 1994) and that just 6 weeks of healing could increase the ability of the anulus to resist a high hydrostatic pressure within the nucleus (Ahlgren et al., 2000). Suturing the anulus lesion had a negligible additional effect on strengthening the anulus over and above the 6 week healing response (Ahlgren et al., 2000). Biological changes observed in disrupted discs (Fig. 6) can be likened to a healing response that is frustrated (in central regions) by the inability of a small cell population to repair an extensive matrix which is repeatedly exposed to new mechanical insults (Ulrich et al., 2007). Frustrated healing (Adams et al., 2009) could explain increased cytokine levels, and the increased activity of matrix-degrading enzymes, including the MMPs (Antoniou et al., 1996a) and ADAMTSs (Le Maitre et al., 2004), which are concentrated in the vicinity of structural defects (Weiler et al., 2002).

6.3. Healing of the nucleus

Enzymatic reduction of proteoglycans in the nucleus of young dogs induced a healing response that largely restored disc height and proteoglycan concentration by 32 weeks (Melrose et al., 1996). Restoring proteoglycan content increased hydration and fluid pressure within the disc, and these two factors appeared to cause blood vessels to regress so that further internal healing was inhibited. In contrast, partial nucleotomy in mature pigs leads to fibrosis and scar formation after several weeks, followed by progressive height loss over the following months (Omlor et al., 2009). Steady deterioration in the pig discs could be due to the fact that nucleotomy required a substantial incision into the anulus as well as a reduction in nucleus volume. True healing of the nucleus appears to be limited by low cell density, rather than by movement of disrupted tissues, because surgical stabilisation of an injured disc to prohibit movement did not alter the healing pattern (Moore et al., 1994). Lumbar intervertebral discs are the largest avascular structures in the human body, and nutrients reach the disc centre primarily as a result of diffusion from blood vessels in the endplate and peripheral anulus (Urban et al., 2004). A lack of glucose can kill some disc cells (Junger et al., 2009) and probably explains why disc cell density declines during growth (Liescher et al., *in press*) as metabolite transport difficulties increase. Consequently, cell density in the adult disc nucleus is critically low, and any disturbance to normal metabolism (such as sclerosis of the bony endplate, or smoking cigarettes) may be sufficient to kill cells and precipitate degenerative changes (Urban et al., 2004; Battie et al., 1991). Certainly, the adult disc cell population is too small to have much effect in turning-over the highly cross-linked collagen network of the matrix, and collagen half-life (“turnover time”) in adult human discs is more than 100 years (Sivan et al., 2008). This is a sufficient explanation for lack of healing in the inner anulus and nucleus.

6.4. Anulus “vs” nucleus

Nutritional problems faced by cells in the disc centre are often emphasised, because this is where the adverse consequences of ageing first become apparent. Unfortunately, this has caused the relatively high cell density and nutrient supply to the outer anulus to be overlooked. The outer anulus has a four-fold greater cell density than the nucleus (Hastreiter et al., 2001), presumably because its cells are well supplied by capillaries on the disc surface, and because metabolite transport here is augmented by fluid flow into and out of

the disc periphery (Ferguson et al., 2004; McMillan et al., 1996). The high metabolic potential of the outer anulus explains why its mechanical properties match those of adjacent vertebrae, whereas the inner and middle anulus appear to be less able to adapt to mechanical demands (Skrzypiec et al., 2007). The proximity of the outer anulus to blood vessels has another advantage when it comes to healing: it allows blood-borne cells to promote neovascularisation and tissue remodelling.

6.5. Healing of the vertebral endplate

Little is known about endplate healing following injury. Direct perforation of the endplate in young pigs stimulates rebuilding of trabecular bone, and proliferation of cartilaginous tissue around the defect then resembles a Schmorl's node (Holm et al., 2004). The bony endplate and its supporting trabeculae are metabolically active, and in sheep, remodelling follows injury to the outer anulus (Moore et al., 1996) presumably in response to the altered mechanical loading on the bone (Przybyla et al., 2006). Vascular proliferation occurs within the cartilage endplate near a peripheral disc lesion in an apparent attempt to boost metabolite transport to the injury site in the disc (Moore et al., 1992). In humans, degenerated (and presumably disrupted) discs exhibit a proliferation of blood vessels and sensory nerves in the endplate (Brown et al., 1997), accompanied by increased collagen denaturation and synthesis which are indicative of a remodelling or healing response (Antoniou et al., 1996b).

6.6. Disc healing and pain relief

The above evidence suggests that treatment for discogenic pain should be directed towards the disc periphery (Fig. 5A), with the aim of reducing inflammation and re-establishing a physical barrier between nucleus pulposus, and nerve cells in the outer anulus, vertebral endplate, and nerve roots. Such a barrier could reduce discogenic back pain even if it did little to reverse age-related biochemical changes in the nucleus. We know already that an intact outer anulus predicts centralisation of back pain (Donelson et al., 1997) and this in turn is associated with a reduced risk of chronic back pain (Werneke and Hart, 2001) and increased return to work (Karas et al., 1997).

7. Stimulation of disc healing

This subject has long been neglected, with researchers paying more attention to disc ageing, degeneration and “regeneration”. However, tendons and ligaments have similar cells and matrix composition to the outer anulus, and they appear to heal in a broadly similar manner, involving neovascularisation and neoinnervation (Wang, 2006). Large tendons also have similar metabolite transport problems as the disc. Techniques for promoting tendon and ligament healing may therefore be applicable to the disc also, especially in the early stages of disc failure, before the structure of the anulus is destroyed. Of course, analogies between disc and tendon healing should not be taken too far: collagen fibres and blood vessels within tendons are compartmentalised by fine collagenous sheaths (the endotenon) which have not been described in the disc; metabolite transport problems will be greater in the disc than in even the largest tendon; and it is much more difficult to unload a disc than a tendon. Nevertheless, the following sections explore the possibility that disc and tendon healing have much in common.

7.1. Inflammatory phase

A major principle of tendon healing is to avoid re-injury during the initial inflammatory phase, which typically lasts for a few days and is dominated by the activity of blood-borne cells (Wang, 2006). Failure

to rest during this time increases the risk of developing a chronic degenerative tendinosis (Wang, 2006). Initial immobilisation is also important for healing of ligament ruptures (Edson, 2006). Similar principles should apply to the disc, because repeated minor injuries to the annulus of small animals greatly prolong the inflammatory reaction and “enhance” degeneration (Ulrich et al., 2007). Repeated endplate injuries in pigs likewise exaggerate subsequent degeneration (Cinotti et al., 2005). To suggest that a patient should rest an injured back may appear to be at odds with current attempts to de-medicalise back pain, but it is not. Psychosocial factors have little influence on the initiation of severe back pain (Adams et al., 1999), and chronic back pain always starts as acute back pain. The originator of the Biopsychosocial Model of back pain has since warned that physical causes of back pain should not be neglected (Waddell, 2002). Certainly it makes good biological sense to avoid physical exacerbation of a disc injury, and there is some evidence from a sheep study that limiting motion can facilitate healing of the annulus (Latham et al., 1994). In humans, stretching of the outer annulus is greatest in the early morning when discs are swollen with fluid (Adams et al., 1987) and avoiding early morning flexion has been shown to reduce recurrent attacks of back pain (Snook et al., 2002).

7.2. Reparative phase

A second principle of tendon healing is to introduce controlled mobilisation during the second (reparative) phase of healing, during which the native fibroblasts repair the collagen matrix (Wang, 2006). Repeated gentle stretching of cultured fibroblasts stimulates collagen I synthesis (Lee et al., 2004), improves their alignment (Neidlinger-Wilke et al., 2001) and inhibits tendon neovascularisation (Nakamura et al., 2008). Early passive mobilisation after tendon repair prevents scarring and adhesions (Adolfsson et al., 1996) and eccentric exercise can also be beneficial (Ohberg et al., 2004). Passive cyclic spinal flexion could similarly stimulate repair of the outer posterior annulus and longitudinal ligament. Experiments on mice have shown that static stretching of the annulus reduces degenerative changes following a compressive overload insult (Lotz et al., 2008) suggesting that tension protects collagen fibres from enzymatic degradation (Nabeshima et al., 1996). Controlled spinal flexion could also prevent spinal tissues from healing with a shortened length, with a consequent risk of re-injury. Performing cyclic spinal flexion while lying on one side would minimise spinal compressive loading, and hence reduce the risk of nucleus pulposus being squeezed into the healing peripheral annulus (Adams and Hutton, 1985; Tampier et al., 2007; Pezowicz et al., 2006). Torsional movements of the spine increase tension in half of the layers of the annulus (Krismer et al., 1996) so a rotational mobilisation might facilitate inter-lamella movements and prevent extensive scarring. In clinical practice, controlled mobilisation of a recently-injured spinal level can be difficult due to pain and muscle spasm, but manual therapy can help to reduce pain and normalise muscle tone (Boal and Gillette, 2004) and thereby decrease stress concentrations in the disc. Gentle early mobilisation could also benefit the bony endplate, because repetitive micromovement stimulates fracture healing in adult long bones (Kenwright et al., 1991).

7.3. Remodelling phase

Mobilisation can continue into the final (“remodelling”) phase of tendon healing which starts at about 6 weeks, and which improves the alignment, organisation and cross-linking of collagen fibres (Wang, 2006). During this period, there is a reduction in cellularity (Lui et al., 2007) and regression of blood vessels (Chamberlain et al., 2009) as the tissue matures from granulation to scar tissue. Eccentric exercise (but not concentric) can help to reduce vascularity, and stretching also increases the collagen content and biomechanical

properties of tendons (de Almeida et al., 2009). Vigorous stretching exercise can reduce pain in degenerative tendinosis (Alfredson et al., 1998) and soft tissue mobilisation promotes tendon healing and fibroblast proliferation in animals (Gehlsen et al., 1999). These animal experiments suggest that disc remodelling in patients might be improved by repetitive spinal movements, but the optimum levels of movement and loading are unknown. Cell and tissue culture studies show that moderate cyclic loading has anabolic effects on disc cells, whereas catabolic effects predominate when loading is static or outside normal physiological limits (Ishihara et al., 1996; Wuertz et al., 2009). Simulated physical therapy techniques can create osteogenic levels of strain in animal bones (Wilson et al., 1999) and increase the proliferation of human fibroblasts (Meltzer and Standley, 2007). However, further work is required to quantify the loading and movement required to optimise disc healing during each of the three phases described above.

7.4. Boosting disc metabolism

Some other possibilities for improving healing are specific to the disc. Proteoglycan synthesis in the nucleus is limited by cell density, which in turn appears to be limited by metabolite transport difficulties. Metabolite transport is enhanced by fluid flow arising from alternating periods of rest and activity, which cause a 20% diurnal change in disc water content (McMillan et al., 1996; Botsford et al., 1994). For cells in the nucleus, the effect of fluid flow may be important only for large molecules which diffuse slowly (Ferguson et al., 2004), and boosting cell metabolism beyond the capabilities of metabolite transport is likely to be futile (Kobayashi et al., 2008). However, load-induced fluid flow could have a large influence on the outer annulus and endplate because these regions experience a large fluid flux (Ferguson et al., 2004) and have “first use” of nutrients carried along with it.

Nutrient transport in dog discs is enhanced by long-term exercise (Holm and Nachemson, 1983) and hindered by fusion (Holm and Nachemson, 1982). Activity could also help to wash-out metabolic waste products, degrading enzymes, and cytokines. This could explain why daily distraction of rabbit discs can rehydrate the nucleus and up-regulate gene expression for collagens and proteoglycans (Guehring et al., 2006). In patients with back pain, a single session of lumbar joint mobilisation has been shown to increase water diffusion within a degenerated nucleus pulposus (Beattie et al., 2009). Alternating periods of full lumbar flexion and extension could have a similar effect, because different postures expel water differently from different parts of the disc (Adams and Hutton, 1983) and hence would boost overall fluid exchange. Even running can stimulate disc cell metabolism, in rats (Wei et al., 2009).

7.5. Technological interventions

Various technologies could possibly be employed to aid disc healing and alleviate discogenic pain. Sclerosing agents sometimes reduce neovascularisation and pain in tendon (Zeisig et al., 2010) and could possibly have a similar effect on discs. Their ability to stimulate fibrous tissue growth (Dagenais et al., 2005) may also counter the instability associated with disc degeneration (Zhao et al., 2005; Latham et al., 1994). Surgical patches of synthetic material, held in place by biological ‘glue’, have been used to repair dural tears by encouraging the formation of a collagenous “waterproof” membrane (Shibayama et al., 2008). Similar patches could possibly be used to treat recurrent sciatica by sealing a radial fissure on the disc surface, using fibrin as the glue (Buser et al., 2009). The possibilities of tissue engineering techniques being used to promote annulus repair have recently been reviewed (Melrose et al., 2008). Healing of the vertebral endplate could possibly be accelerated by bone morphogenic proteins, which stimulate spinal fusion (White et al., 2007) while also

benefiting the disc (Yoon et al., 2004). Other drugs appear to enhance blood flow in the vertebral endplate and so have the potential to stimulate healing of the disc and endplate (Rajasekaran and Venkatadass, 2008).

7.6. Patient selection

The success or failure of any therapy for back pain depends on correct identification of the pain source. Provocation discography can be used to identify discogenic pain (Schwarzer et al., 1995; Peng et al., 2010) and even to localise it to the peripheral annulus or endplate (Peng et al., 2009b) but this technique carries some risk to the patient (Carragee et al., 2009). Unfortunately, there are no clinical methods that would enable physical therapists to identify discogenic back pain with confidence (Hancock et al., 2007). Nevertheless, the following research-based suggestions may assist in the development of such methods. The outer posterior annulus is more likely to be the pain source if one or more of the following is applicable: a) there is a complete (leaking) posterior radial fissure (Videman and Nurminen, 2004), b) MRI reveals a “high intensity zone” (Peng et al., 2006b), c) symptoms are precipitated by high spinal loading in flexion (Adams et al., 2000a), d) pain is provoked by stretching the posterior annulus in full flexion or axial rotation (Krismer et al., 1996), or e) pain is worse in the early morning (Adams et al., 1987). An endplate is more likely to be the source of pain if one or more of the following is applicable: a) there is a Schmorl's node (Peng et al., 2009b) (Hamanishi et al., 1994) or Modic changes (Kjaer et al., 2006) visible on MRI, b) symptoms are exacerbated by compressive loading (Brinckmann et al., 1989) or c) the patient has low bone mineral density (Melton et al., 2007). In all cases, pain should be relieved by reducing spinal load, for example by lying down, or by adopting the “all 4's” (hands and knees) posture which minimises load while allowing relatively free movement (McGill, 2007). Pain from the outer posterior annulus would more likely show a directional preference: it would be provoked more by flexion (which stretches the wound) than by extension, when it might be protected by load transfer to the neural arch (Adams et al., 2000b). Finally, endplate injuries are more likely to cause back pain in their acute stage (Takahashi et al., 1995) whereas pain from a radial fissure may be gradual in onset (Adams and Hutton, 1985).

We suggest that rehabilitation protocols should reflect these different pain sources. In the case of a radial fissure, controlled mobilisation could initially be directed towards the direction that decreases the pain. Then, after scar formation, stretching would be directed towards the direction that provokes the pain in order to promote remodelling of the fibrous tissue. An endplate fracture would be treated (as any fracture) with initial unloading followed by progressive reloading of the tissue, possibly combined with intermittent traction.

8. Conclusions

It is time to study intervertebral disc healing in its own right, and not equate it with the separate (and more difficult) problem of trying to reverse age-related disc degeneration. Physical therapists traditionally employ mechanical loading as a healing stimulus, and could take a leading role in devising and evaluating therapies to relieve discogenic back pain by promoting healing in the disc periphery.

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