The pathogenesis of discogenic low back pain

B. Peng,
W. Wu,
S. Hou,
P. Li,
C. Zhang,
Y. Yang

From 304th Hospital, Beijing, People's Republic of China

Discogenic low back pain is a common cause of disability, but its pathogenesis is poorly understood. We collected 19 specimens of lumbar intervertebral discs from 17 patients with discogenic low back pain during posterior lumbar interbody fusion, 12 from physiologically ageing discs and ten from normal control discs. We investigated the histological features and assessed the immunoreactive activity of neurofilament (NF200) and neuropeptides such as substance P (SP) and vasoactive-intestinal peptide (VIP) in the nerve fibres.

The distinct histological characteristic of the painful disc was the formation of a zone of vascularised granulation tissue from the nucleus pulposus to the outer part of the annulus fibrosus along the edges of the fissures. SP-, NF- and VIP-immunoreactive nerve fibres in the painful discs were more extensive than in the control discs. Growth of nerves deep into the annulus fibrosus and nucleus pulposus was observed mainly along the zone of granulation tissue in the painful discs. This suggests that the zone of granulation tissue with extensive innervation along the tears in the posterior part of the painful disc may be responsible for causing the pain of discography and of discogenic low back pain.

Discogenic low back pain is non-radicular and occurs in the absence of spinal deformity, instability and signs of neural tension.[1] It arises from the disc itself[2] and the mechanism of its production is uncertain.

In the absence of evidence of disc pathology on radiological and CT images, it may be impossible to localise a painful disc from the symptoms and the signs elicited on physical examination. Although MRI may identify a degenerative disc (a 'black disc'), it will not differentiate between a disc which is pathologically painful and one which is physiologically ageing.[3] Intervertebral disc degeneration is commonly seen on MRI in asymptomatic subjects.[4-6] Discography is the most important test for diagnosing discogenic back pain. Some believe that discography, when carefully done and interpreted, is highly specific with a false-positive rate of 0%.[7] However, controversy remains as to the accuracy and specificity of discography because of the inability to understand the mechanism which produces the pain. That provoked by the injection of contrast medium into the disc may be difficult to relate to the images seen after discography. The key feature of discography is the reproduction of the pain felt by the patient on stimulation of the disc.[8] Studies have shown that reproduction of the pain is associated with tears which extend to the outer region of the annulus fibrosus.[9-11] This suggests that the origins of the pain in discography may lie in abnormalities of the structure of the disc. In particular, the pain may arise from the tears and surrounding structures into which the contrast medium leaks from the nucleus pulposus into the outer zone of the annulus fibrosus. Thus, discography may be helpful in understanding the pathophysiology of discogenic low back pain.

The contrast-enhanced axial view of CT after discography allows visualisation of the tears in the painful disc. With this information we have been able to localise and excise *en bloc* specimens of the torn annulus of a painful disc during posterior lumbar interbody fusion for discogenic low back pain (Fig. 1). Consecutive slices of the excised specimen have been studied histologically and immunohistochemically to explore the intrinsic relationship between the pathological lesions and the surrounding innervation in a painful disc.

The distribution of nerve fibres in the different parts of the human disc has been previously described.[12-14] The nerve fibres may contain nociceptive neurotransmitters such as substance P (SP), calcitonin-gene-related peptide (CGRP), and vasoactive intestinal peptide (VIP).[15-18] However, there has been no description of nerve ingrowth along the tears or fis-

■ B. Peng, MD, PhD, Orthopaedic Surgeon, Associate Professor
■ W. Wu, MD, Orthopaedic Surgeon, Professor
■ S. Hou, MD, Orthopaedic Surgeon, Professor
■ C. Zhang, MD, Lecturer
Department of Orthopaedics
■ P. Li, MD, Anaesthetist, Lecturer
Department of Anaesthesiology
■ Y. Yang, MD, Lecturer
Department of Pathology
304th Hospital, 51 Fucheng Road, Beijing 100037, People's Republic of China.

Correspondence should be sent to Dr B. Peng.

doi:10.1302/0301-620X.87B1.15708 $2.00

J Bone Joint Surg [Br] 2005;87-B:62-7.
Received 18 November 2003; Accepted after revision 12 July 2004

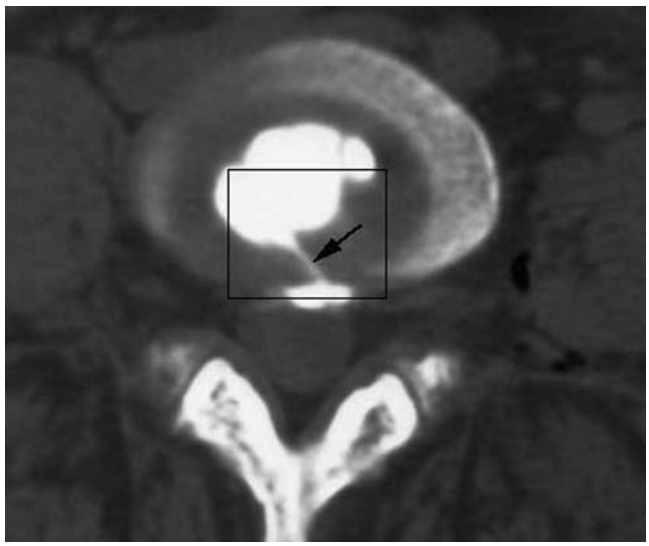

Fig. 1

CT of a tear after discography (arrow). The rectangle indicates the amount of disc excised for histological examination.

sures in a painful disc. Our aim was to investigate the pathological changes in and the innervation of painful discs in order to understand the cause and the mechanism of primary discogenic low back pain.

Patients and Methods

We examined 19 specimens of lumbar discs taken from 17 consecutive patients with disabling discogenic low back pain who underwent excision of the disc and posterior lumbar interbody fusion (PLIF). There were 12 men and five women, with a mean age of 36 years (19 to 55). The mean duration of low back pain was 29 months (8 to 120). Six patients had a history of lumbar injury. All had conventional radiography and MRI of the lumbar spine. None had symptoms or signs of radicular pain and disc herniation was not seen on MRI. All the patients had discography before operation. A positive discogram was seen in a patient with an annular tear who had a severe concordant pain response. After discography, CT was performed to localise the tear in the painful disc. In the 19 painful discs, there were 17 annular tears occurring posteriorly or posterolaterally and two seen both anteriorly and posteriorly. The signal intensity on T2-weighted MRI was decreased in 18 of the painful discs, with only one appearing to be relatively normal.

For a normal control group we obtained ten specimens from the posterior parts of disc tissue at L4-L5 and L5-S1 from five fresh cadavers with a mean age of 39 years (22 to 45), who had had no history of low back pain during their lifetime. All these discs appeared to be normal macroscopically with no protrusion or bulging. Specimens of non-painful and macroscopically normal lumbar discs, with decreased intensity of T2-weighted sequences on MRI, were harvested from 12 patients with a mean age of 44 years (29 to 61) who had undergone extensive decompression and PLIF, to act as a physiologically ageing control group. Ten of these patients had stenosis of the lumbar canal and complained of intermittent claudication with or without mild low back pain. Another two had a schwannoma in the lumbar spinal canal. No protrusion or bulging of the disc was found macroscopically during these operations.

In order to assess the morphological features and innervation precisely, all the specimens included the nucleus pulposus, the annulus fibrosus and the posterior longitudinal ligament in continuity.

Conventional histological examination and immunohistochemical analysis. The specimens were fixed in 10% neutral formalin, embedded in paraffin, slit sagittally and sliced into serial sections 5 μm thick. Serial sections were stained with haematoxylin and eosin and subjected to immunohistochemical analysis. Monoclonal antibody to neurofilament (NF200) and polyclonal antibodies to SP and VIP were used to help to clarify the innervation of the discs.

The sections were dewaxed and endogenous tissue peroxidase activity was quenched by soaking them for 30 minutes at room temperature with 0.3% H_2O_2 solution in distilled water. They were then treated with 5% goat serum in phosphate-buffered saline (PBS) for ten minutes to block non-specific binding. After rinsing with buffer, the primary monoclonal antibody to NF200 (diluted 1:50, mouse monoclonal IgG; Dako, DK-2600 Glostrop, Denmark), and the primary polyclonal antibodies to SP and VIP (diluted 1:100, rabbit polyclonal antibodies; Zymed, San Francisco, California) were applied, and the sections incubated for 60 minutes at 37°C, and rinsed with PBS. Biotinylated goat anti-mouse IgG (diluted 1:200) and goat anti-rabbit secondary antibodies (diluted 1:200) were used for NF primary monoclonal antibody and neuropeptides SP and VIP primary polyclonal antibodies, respectively. After further rinses with buffer, streptavidin peroxidase was used for incubation at 37°C for 30 minutes and then after rinsing with buffer, 3.3' diaminobenzidine was used. Finally, the sections were counterstained with haematoxylin, rinsed with running tap water, dehydrated in ethanol, cleared in xylene, and mounted. Control sections were stained in the same way, omitting only the specific primary antibodies.

Results

Histological examination. In the normal control specimens, the annulus fibrosus consisted of the normal lamellar structure of collagen fibres. The nucleus pulposus showed sparse collagen fibres with a single cartilage cell or an island of a few cells surrounded by a capsule. Blood vessels were seen in the posterior longitudinal ligament and the outermost layers of the annulus fibrosus. In the specimens of physiologically ageing discs, the lamellar structures of the annulus fibrosus were arrayed relatively regularly, and, in some

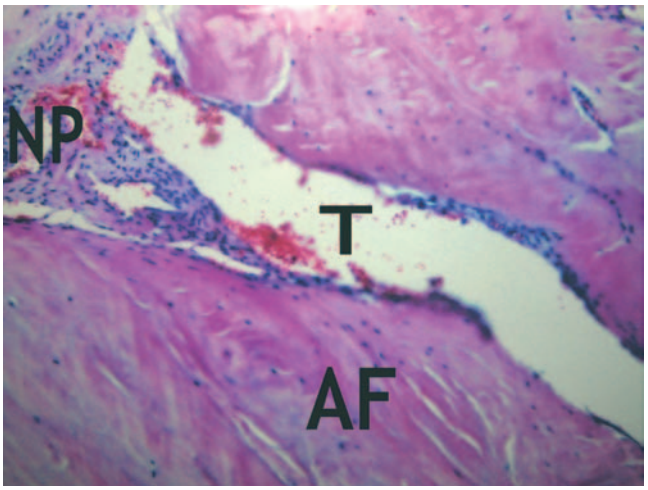

Fig. 2a

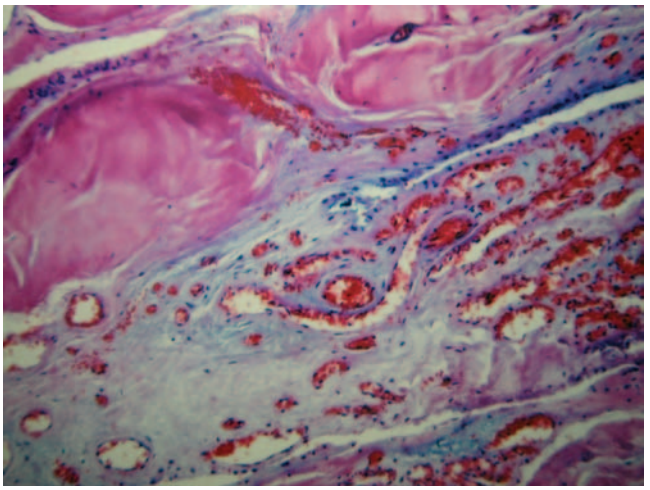

Fig. 2b

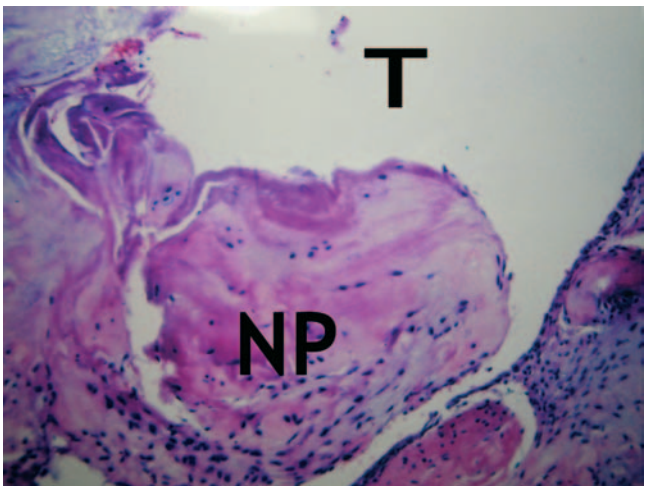

Fig. 2c

Photomicrographs of a painful disc. Figure 2a – This shows a radial tear (T) and the surrounding tissue in the junction between the zone of nucleus pulposus (NP) and the annulus fibrosus (AF) where the formation of granulation tissue is seen (x130). Figure 2b – This shows vascularised granulation tissue in the annulus fibrosus (x130). Figure 2c – The tear leads to the nucleus pulposus (NP) in which fibrosis and the formation of granulation tissue are seen (haematoxylin and eosin; x270).

samples, disrupted and confused lamellar structures were seen in the middle and inner layers of the annulus fibrosus. In the nucleus pulposus, there was increased density of the matrix and the formation of clusters of chondrocytes. The distinction between the nucleus pulposus and the inner annular fibrosus became blurred, and there was a tendency for this to become more evident with increasing age.

In the specimens of painful discs from the patients with discogenic low back pain, the most notable feature was the formation of a zone of vascularised granulation tissue which extended from the nucleus pulposus to the outer region of the annulus fibrosus along the tears shown on CT after discography (Fig. 2). The degree of maturation of the granulation tissue varied. The zone was approximately 0.1 to 5 mm in sagittal width and contained one or several fissures. The adjacent tissues surrounding the tears in the posterior part of the nucleus pulposus and the annulus fibrosus were replaced by disorganised and vascularised granulation and scar tissue. The lamellar structure of the annulus fibrosus adjacent to the zone of granulation tissue was arrayed relatively regularly, becoming disrupted and confused. The structure of the annulus fibrosus distant to this zone was relatively normal. Extensive vascularity was seen in the outer layers of the annulus fibrosus. The distinction between the nucleus pulposus and the inner annulus fibrosus had disappeared. In the nucleus pulposus, fibrosis and increased density of the matrix were observed. The round chondrocytes were transformed into oval fibroblasts.

Immunohistochemical examination for innervation. The number and percentage of SP-, NF- and VIP-immunoreactive nerve fibres in the specimens of control discs, ageing discs, and painful discs varied (Table I). By observing consecutive tissue sections, specific immunoreactivity to NF, SP and VIP was seen in the same nerve fibres. When NF immunoreactivity was observed, a response to one or both of the two neuropeptides was seen simultaneously. Both bundles of nerve fibres and free fibres were seen in the painful and control discs, and myelinated and unmyelinated free fibres were identified. Some immunoreactive dots may have been images of cross-sections of nerve fibres. No immuno-

Table I. SP-, NF- and VIP-immunoreactive fibres in the groups of discs, by number and *percentage* (C, normal control disc (10); A, ageing disc (12); and P, painful disc (19))

	SP			NF			VIP		
Area*	**C**	**A**	**P**	**C**	**A**	**P**	**C**	**A**	**P**
PLL	5 (*50*)	9 (*75*)	15 (*79*)	10 (*100*)	12 (*100*)	19 (*100*)	4 (*40*)	7 (*58*)	9 (*47*)
Outer 1/3 in AF	3 (*30*)	5 (*42*)	12 (*63*)	4 (*40*)	7 (*58*)	16 (*84*)	2 (*20*)	4 (*33*)	7 (*37*)
Inner 2/3 in AF	0	0	6 (*32*)	0	2 (*17*)	9 (*47*)	0	0	2 (*11*)
NP	0	0	4 (*21*)	0	0	6 (*32*)	0	0	0

* PLL, posterior longitudinal ligament; AF, annulus fibrosus; NP, nucleus pulposus

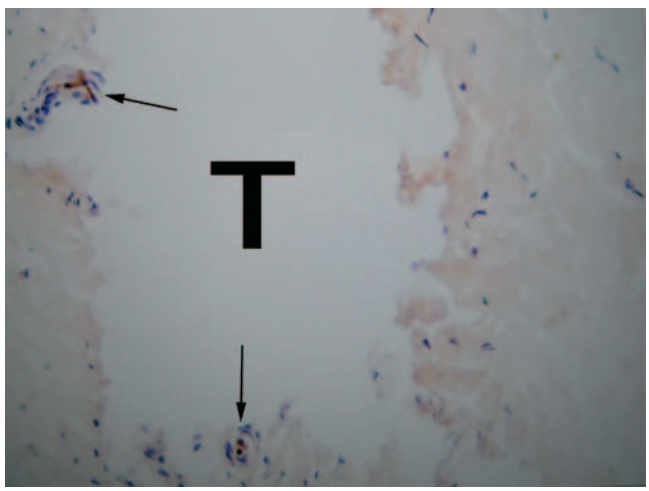

Fig. 3a

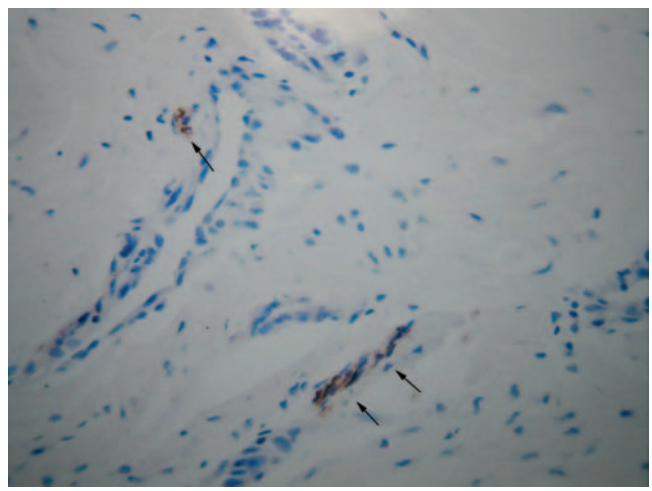

Fig. 3b

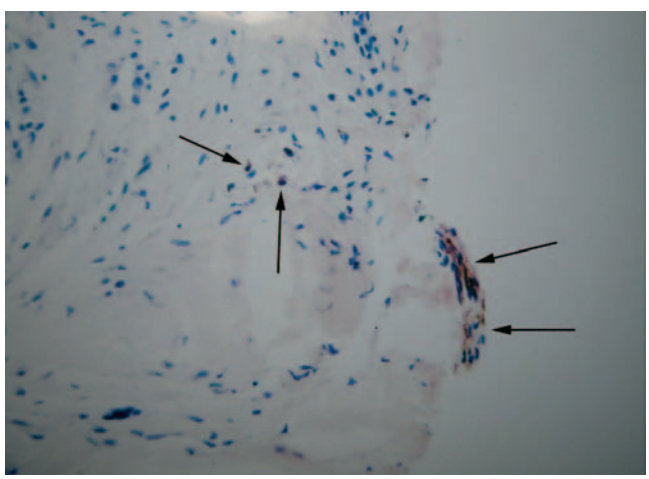

Fig. 3c

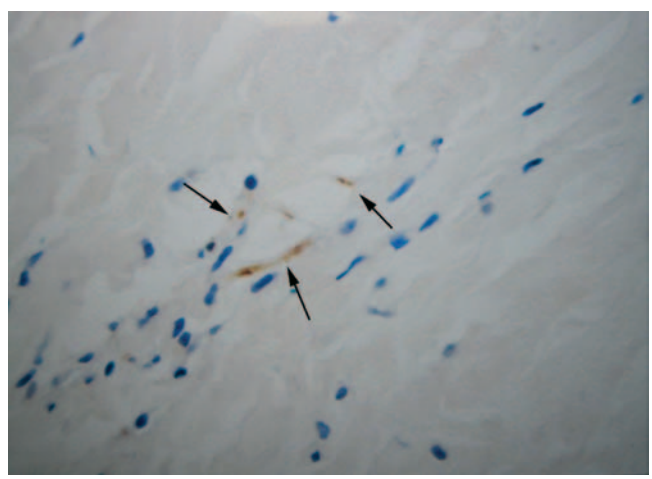

Fig. 3d

Photomicrographs showing evidence of innervation in painful discs. Figure 3a – SP-immunoreactive nerve fibres (arrows) are present in the margin of the tear (T) within the annulus fibrosus (x130). Figure 3b – SP-immunoreactive nerve fibres (arrows) are seen in the granulation tissue within the nucleus pulposus (x130). Figure 3c – NF-immunoreactive nerve fibres (arrows) are present in the margin of the tear within the annulus fibrosus (x130). Figure 3d – VIP-immunoreactive nerve fibres (arrows) are present in the annulus fibrosus (haematoxylin and eosin; x270).

reactive structures were seen in the sections treated with normal serum only, in the absence of primary antibody.

In all the control, ageing, and painful discs, the posterior longitudinal ligaments contained NF-staining nerve fibres. In control discs sparse nerve fibres were seen only in the outermost layers of the annulus fibrosus. Positive staining for SP was present in three (30%) of the ten control specimens, for NF in four (40%), and for VIP in two (20%). Occasionally, VIP-immunoreactive fibres were found adjacent to blood vessels. Positive staining for SP, NF, and VIP increased in the specimens of the ageing discs and those which were painful. In the ageing discs, NF-positive stain-

ing nerve fibres were observed growing into the inner annulus fibrosus in two (17%), but SP and VIP fibres were neither seen in the deeper part of the annulus fibrosus nor in the nucleus pulposus. Such ingrowth into these deeper sites in painful discs occurred mainly along the zone of granulation tissue around the tears (Fig. 3). SP- and NF-immunoreactive fibres were present in the margin along the tears. In the painful discs, positive staining for SP and NF in the nucleus pulposus was observed in four (21%) and six (32%), respectively, showing ingrowth of nerve into the nucleus pulposus, but no VIP-positive staining was noted.

Discussion

Many studies have suggested that nerve fibres are present in the longitudinal ligaments and in the outer layers of the annulus fibrosus.[12-14] An immunohistochemical study demonstrated the presence of SP-immunoreactive fibres in the posterior longitudinal ligament and the presence of SP-, CGRP-, and VIP-immunoreactive nerve fibres has been demonstrated in animal and human intervertebral discs.[15-18] However, these studies were only carried out on normal lumbar discs. There have been further investigations concerning the innervation of discs in the patients with low back pain.[19-22] These were on specimens harvested from the anterior aspect of painful discs, in which tears or fissures in the annulus fibrosus are rarely seen on discography. Hence, these investigations were not able to define accurately the structures from which low back pain and the pain provoked by discography may originate.

Studies by CT after discography have suggested that the contrast media leaks from the nucleus pulposus to the posterior part of the annulus fibrosus along the tears in painful discs[9] and therefore may be attributable to weakness in the posterior annulus fibrosus.[23] Previous studies have indicated that pain induced by discography is associated with tears which extend to the outer zone of the annulus fibrosus.[9,11] Our study examined specimens of painful discs taken from the posterior part of the annulus, including tears shown on CT after discography.

There are two theories concerning the mechanism of pain on discography.[24] One attributes this to the stimulation of nociceptive fibres in the innervated part of the annulus fibrosus, the vertebral end plate or body, which may cause pain as the injection increases intradiscal pressure.[25] Another view is that injection leads to chemical stimulation which induces pain.[26] Our study clearly indicated that the tears seen at discography were associated with a zone of vascularised granulation tissue containing abundant SP-immunoreactive nerve fibres which had been thought to be nociceptive. We feel that the pressure stimuli caused by injection of the contrast directly stimulates the nociceptors within the granulation tissue, inducing pain. This pain settles immediately after the pressure declines as the contrast media leaks out of the disc from the tears. The inflammatory granulation tissue produces proinflammatory cytokines and mediators such as prostaglandin E_2, interleukin (IL)-6 and IL-8 which can sensitise the nociceptors within the painful discs.[27] Once acted on by a painful substance, the threshold for mechanical stimulation of the nociceptors may be lowered, and physical loading within the physiological range of the disc may cause pain. The nociceptors within the granulation tissue would be the most likely to be affected by local inflammation producing a painful response from the fissure in the annulus. During discography, pain may occur when the intradiscal pressure increases sharply as the contrast medium is injected into the disc. Our findings suggest that pain may arise from the nucleus pulposus due to innervation accompanying the ingrowth of granulation tissue. An extensive network of nerve fibres was seen in the posterior part of the annulus fibrosus in the ageing discs, but there was no pain since there were no tears and no surrounding granulation tissue in this region of the annulus fibrosus.

A normal disc should have a bright appearance on MRI, whereas a dehydrated disc appears dark. The latter may be the earliest stage of degenerative disc disease.[3,6] However, it may reflect the normal physiological process of ageing and not be associated with any disease process.[4,5] Abnormalities of the disc are commonly seen on MRI in asymptomatic subjects. Modic et al[28] found that an abnormal signal intensity was present in 30% of the discs in asymptomatic volunteers. It is difficult to distinguish the ageing disc from the pathological disc but the presence of a zone of vascularised granulation tissue accompanying the nociceptors along the tears of the annulus fibrosus is an almost constant finding in a pathological disc.

Of the 17 patients with discogenic low back pain in our study, six were adults below the age of 30 years. It is unlikely that the changes in their discs were age-related, but injury to the posterior annulus fibrosus may have played a role in their pathogenesis. Structurally, the weak posterior part of the annulus fibrosus may be subjected to damage, and it is a consistent site for tears shown on discography. Different animal models of the annular defect have shown that the healing is defective and probably initiates degeneration of the disc.[29-32] The tears demonstrated at the periphery of the annulus fibrosus may play a critical role in discogenic low back pain and the initiation of degenerative changes. The formation of vascularised granulation tissue may be a physiological response to repair the injury to the annulus. However, because of the poor blood supply and the high tensile stress, inadequate healing seems to be inevitable. Immunoreaction and the recruitment of inflammatory cells may impede healing further, and the ingrowth of vascularised granulation tissue into the disc may produce growth factors and cytokines which may modulate the differentiation of cells such as chondrocytes in the nucleus pulposus. These may be transformed into fibroblasts leading to degeneration of the disc. In some patients these changes may be the principal cause of this back pain, and may be a contributory factor in other patients.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References

1. **Rhyne AL, Smith SE, Wood KE, Darden BV.** Outcome of unoperated discogram-positive low back pain. *Spine* 1995;20:1997-2000.
2. **Mooney V.** Where is the pain coming from? *Spine* 1987;12:754-9.
3. **Buirski G, Silberstein M.** The symptomatic lumbar disc in patients with low-back pain: magnetic resonance imaging appearances in both a symptomatic and control population. *Spine* 1993;18:1808-11.
4. **Jensen MC, Brant-Zawadzki MN, Obuchowski N, et al.** Magnetic resonance imaging of the lumbar spine in people without back pain. *N Engl J Med* 1994;331:69-73.
5. **Powell MC, Wilson M, Szypryt S, Symonds EM, Worthington BS.** Prevalence of lumbar disc degeneration observed by magnetic resonance in symptomless women. *Lancet* 1986;2:1366-7.
6. **Horton WC, Daftari TK.** Which disc as visualized by magnetic resonance imaging is actually a source of pain?: a correlation between magnetic resonance imaging and discography. *Spine* 1992;17(Suppl):164-71.
7. **Walsh TR, Weinstein JN, Spratt KF, et al.** Lumbar discography in normal subjects. *J Bone Joint Surg [Am]* 1990;72-A:1081-8.
8. **Schwarzer AC, Aprill CN, Derby R, et al.** The prevalence and clinical features of internal disc disruption in patients with chronic low back pain. *Spine* 1995;20: 1878-83.
9. **Saifuddin A, Braithwaite I, White J, Taylor BA, Renton P.** The value of lumbar spine magnetic resonance imaging in the demonstration of anular tears. *Spine* 1998; 23:453-7.
10. **Ito M, Incorvaia KM, Yu SF, et al.** Predictive sins of discogenic lumbar pain on magnetic resonance imaging with discography correlation. *Spine* 1998;23:1252-60.
11. **Moneta GB, Videman T, Kaivanto K, et al.** Reported pain during lumbar discography as a function of anular ruptures and disc degeneration: a re-analysis of 833 discograms. *Spine* 1994;19:1968-74.
12. **Bogduk N.** The innervation of the lumbar spine. *Spine* 1983;8:286-93.
13. **Kojima Y, Maeda T, Arai R, Shichikawa K.** Nerve supply to the posterior longitudinal ligament and the intervertebral disc of the rat vertebral column as studied by acetylcholinesterase histochemistry. I. Distribution in the lumbar region. *J Anat* 1990; 169:237-46.
14. **Kojima Y, Maeda T, Arai R, Shichikawa K.** Nerve supply to the posterior longitudinal ligament and the intervertebral disc of the rat vertebral column as studied by acetylcholinesterase histochemistry. II. Regional differences in the distribution of the nerve fibres and their origins. *J Anat* 1990;169:247-55.
15. **Liesi P, Gronblad M, Korkala O, Karaharju E, Rusanen M.** Substance P: a neuropeptide involved in low back pain? *Lancet* 1983;1:1328-9.
16. **Konttinen YT, Gronblad M, Antti-Poika I, et al.** Neuroimmunohistochemical analysis of peridiscal nociceptive neural elements. *Spine* 1990;15:383-6.
17. **McCarthy PW, Petts P, Hamilton A.** RT97- and calcitonin gene-related peptide-like immunoreactivity in lumbar intervertebral discs and adjacent tissue from the rat. *J Anat* 1992;180:15-24.
18. **Ahmed M, Bjurholm A, Kreicbergs A, Schultzberg M.** Neuropeptide Y, tyrosine hydroxylase and vasoactive intestinal polypeptide-immunoreactive nerve fibers in the vertebral bodies, discs, dura mater, and spinal ligaments of the rat lumbar spine. *Spine* 1993;18:268-73.
19. **Coppes MH, Marani E, Thomeer RT, Oudega M, Groen GJ.** Innervation of annulus fibrosis in low back pain. *Lancet* 1990;336:189-90.
20. **Coppes MH, Marani E, Thomeer RT, Groen GJ.** Innervation of "painful" lumbar discs. *Spine* 1997;22:2342-9.
21. **Freemount AJ, Peacock TE, Goupile P, et al.** Nerve ingrowth into diseased intervertebral disc in chronic back pain. *Lancet* 1997;350:178-81.
22. **Johnson WEB, Evans H, Menage J, et al.** Immunohistochemical detection of Schwann cells in innervated and vascularized human intervertebral discs. *Spine* 2001;26:2550-7.
23. **Tsuji H, Hirano N, Ohshima H, et al.** Structural variation of the anterior and posterior annulus fibrosus in the development of human lumbar intervertebral disc: a risk factor for intervertebral disc rupture. *Spine* 1993;18:204-10.
24. **Hanley EN Jr, David SM.** Lumbar arthrodesis for the treatment of back pain. *J Bone Joint Surg [Am]* 1999;81-A:716-30.
25. **Brown MF, Hukkanen MVJ, McCarthy ID, et al.** Sensory and sympathetic innervation of the vertebral endplate in patients with degenerative disc disease. *J Bone Joint Surg [Br]* 1997;79-B:147-53.
26. **Weinstein J, Claverie W, Gibson S.** The pain of discography. *Spine* 1988;13: 1344-8.
27. **Burke JG, Watson RWG, McCormack D, et al.** Intervertebral discs which cause low back pain secrete high levels of proinflammatory mediators. *J Bone Joint Surg [Br]* 2002;84-B:196-201.
28. **Modic MT, Pavlivek W, Weinstein MA, et al.** Magnetic resonance imaging of intervertebral disc disease: clinical and pulse sequence considerations. *Radiology* 1984;152:103-11.
29. **Kanerva A, Kommonen B, Gronblad M, et al.** Inflammatory cells in experimental intervertebral disc injury. *Spine* 1997;22:2711-15.
30. **Osti OL, Vernon-Roberts B, Fraser RD.** Anulus tears and intervertebral disc degeneration: an experimental study using an animal model. *Spine* 1990;15:762-7.
31. **Hampton D, Laros G, McCarron R, Franks D.** Healing potential of the annulus fibrosus. *Spine* 1989;14:398-401.
32. **Kaapa E, Han X, Holm S, et al.** Collagen synthesis and types I, II, IV and VI collagens in an animal model of disc degeneration. *Spine* 1995;20:59-6.