Spinal disorders

Basic science

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"All work is as seed sown;
it grows and spreads,
and sows itself anew" [Thomas Carlyle, 1795-1881]

As we rapidly approach the next millennium, the tree of knowledge is acquiring an increasing number of "fruits of knowledge," major achievements, in the spinal basic science research sphere. This is the result of intense research activity in all parts of the world. Let us now glimpse into the amazing world of spinal basic science research. Let us travel along some of the causeways that have opened up to us in this important area of medicine.

Background—where we stand today

Pathophysiology–morphology, biochemistry

Intervertebral disc cells, previously regarded as sluggish participants in intervertebral disc metabolism, may in fact actively contribute to intervertebral disc degeneration, through a production of several harmful bioactive substances (Kang et al. 1997, Rand et al. 1997). Such bioactive substances, when secreted from disc tissue displaced into a juxtaposition with the nerve root or the dorsal root ganglion, may also seriously harm these neural structures and their important functions (Olmarker et al. 1993, Cavanaugh 1995, Takahashi 1995, Takahashi et al. 1996; Olmarker et al. 1996, 1997, Kayama et al. 1996, Muramoto et al. 1997, Nygaard et al. 1997). There are in fact a plethora of bioactive substances (Table) that when released from disc tissue or disc cells could cause such disharmony of normal intervertebral disc and nerve root function (Fig. 1). Kobayashi and coworkers (1993) demonstrated direct continuity between the subarachnoid space and the endoneurial space. Furthermore, as a result of compression, disc herniations break the blood-nerve barrier of affected nerve roots, producing intraradicular edema (Yoshizawa et al. 1991, 1995, Kobayashi et al. 1993). The presently held opinion is that nerve root dysfunction caused by a disc herniation is the result of a combination of mechanical compression and non-mechanical effects

Table. Some bioactive substances that have been demonstrated in herniated disc tissue

Matrix metalloproteinases
Interleukins
Monocyte chemoattractant protein-1 (MCP-1)
Phospholipase-A2
Macrophage inflammatory protein-1
Growth factors
Intercellular adhesion molecule ICAM-1
Lymphocyte function-associated antigen LFA-1
Nitric oxide
Prostaglandin E2
Leukotriene B4
Thromboxane B2

From: Takahashi 1995; Takahashi et al. 1996; Doita et al. 1996; Kanemoto et al. 1996; Kang et al. 1997; Haro et al. 1997; Rand et al. 1997, Nygaard et al. 1997, and others.

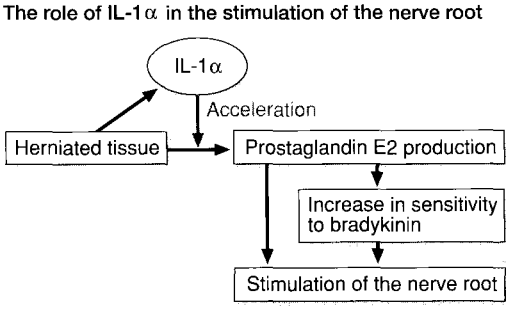

Figure 1. Disturbance of nerve root function may be caused by cytokines secreted from extruded intervertebral disc tissue (Courtesy of Dr. Hiroshi Takahashi, First Department of Orthopaedic Surgery, Toho University School of Medicine, Tokyo, Japan).

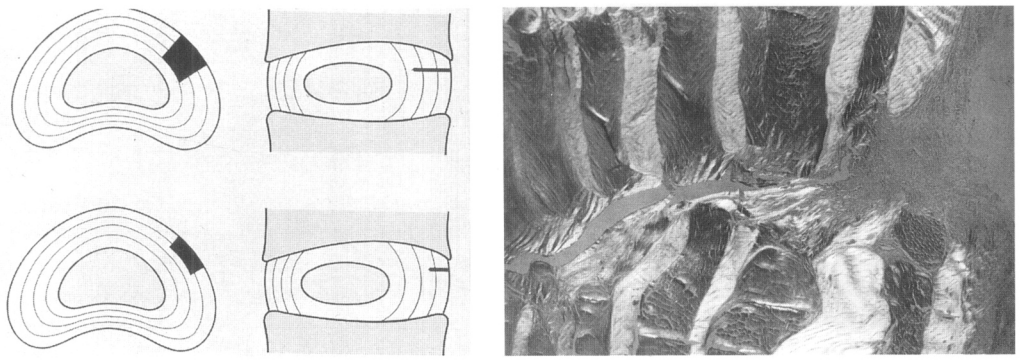

Figure 2. Following an experimental injury of the anterior anulus fibrosus in sheep (left), even when the outer anulus has healed with vascularized granulation tissue, the inner anulus fails to heal (right). Such incomplete healing of the intervertebral disc anulus fibrosus will result in degeneration of the nucleus pulposus and, ultimately, severe degeneration of the entire intervertebral disc (Courtesy of Dr. Orso Osti, a twice Volvo Award winner, Orthopaedic and Spinal Surgery, Harley Chambers, North Adelaide, SA, Australia).

caused by the disc tissue itself (Olmarker and Rydevik 1991). Intraradicular blood vessels have been shown to have a rich innervation by aminergic, cholinergic and peptidergic nerves (Kobayashi et al. 1995), but there is presently no detailed knowledge how all these different vasoregulatory nerves dysfunction as a result of compression and/or direct effects by nucleus pulposus tissue and disc tissue mediators (Takahashi et al. 1996, Doita et al. 1996, Kanemoto et al. 1996). It can be expected that further study in this area will not only increase our understanding of basic pathophysiology, but will also result, sooner or later, in pathophysiology-derived more specific diagnostics and, in particular, treatment.

Another area of great interest focuses on the consequences of intervertebral disc injury. There are several studies (Osti et al. 1990, Fraser et al. 1993, Kääpä 1993) that have shown, in various animal models, that even a seemingly small injury of the outer anular ring will after a while, the time course being somewhat different in various species of experimental animals, result in severe degeneration of the entire intervertebral disc. The mechanism(s) producing this deleterious effect has not been characterized in detail, but it has been shown (Osti et al. 1990) that, following such induced injury, the inner anulus does not heal (Fig. 2). Instead there is progressive failure of the inner anulus, leading to degeneration of the nucleus pulposus (Osti et al. 1990, Fraser et al. 1993). Recently a poorly developed inflammatory response was observed following an induced partial thickness injury of the anulus, which may be a contributing factor to poor healing (Kanerva et al. 1997). Such anulus injury will also alter the phenotype of nucleus pulposus cells, resulting in aberrant collagen production (Kääpä et al. 1994). Similarly in pathological human disc tissue the amount and the distribution of collagen types differ from control disc material (Roberts et al. 1991).

Evidently an anulus injury does not, however, occur as an isolated phenomenon. Recent experimental work by Indahl et al. (1997) has demonstrated functional connections between the intervertebral disc and spinal muscles, multifidus muscles in particular (Fig. 3), and this research group considers it likely that perturbation of an intervertebral disc, e.g. anulus injury, will have a secondary effect on spinal muscles. So when we treat muscle spasm of the spine or otherwise altered muscular function, do we treat the cause or the consequence?

The neural structures present in intervertebral discs have also been analyzed in many studies. Normally the disc is aneural, except for the outer anulus fibrosus (Yoshizawa et al. 1980, Bogduk et al. 1981, 1989). But recent studies (Coppes et al. 1990, 1997, Freemont et al. 1997) have demonstrated an ingrowth of nerves (aberrant innervation) into deeper anulus fibrosus and nucleus pulposus in severely degenerated human discs. This "neoinnervation" appears to be coupled to painfulness of intervertebral discs (Freemont et al. 1997) and may, when clarified somewhat further, explain how discs become painful. Clinically such discs produce a pain response at discography and also when submitted to vibratory stimulation (Yrjämä and Vanharanta 1994). It remains to be established whether such "neoinnervation" can somehow be inhibited and if this will then remove the pain response and the clinical low-back pain symptom. Disc-mediated low-back pain will certainly be the focus of much exciting research during the next decade.

There is also presently a lack of detailed knowledge of the clinical importance of zygapophysial joint-mediated low-back pain. As has been shown by Giles and Harvey (1987a) and Giles and Taylor (1987b) both the capsule and the synovial folds of facet joints

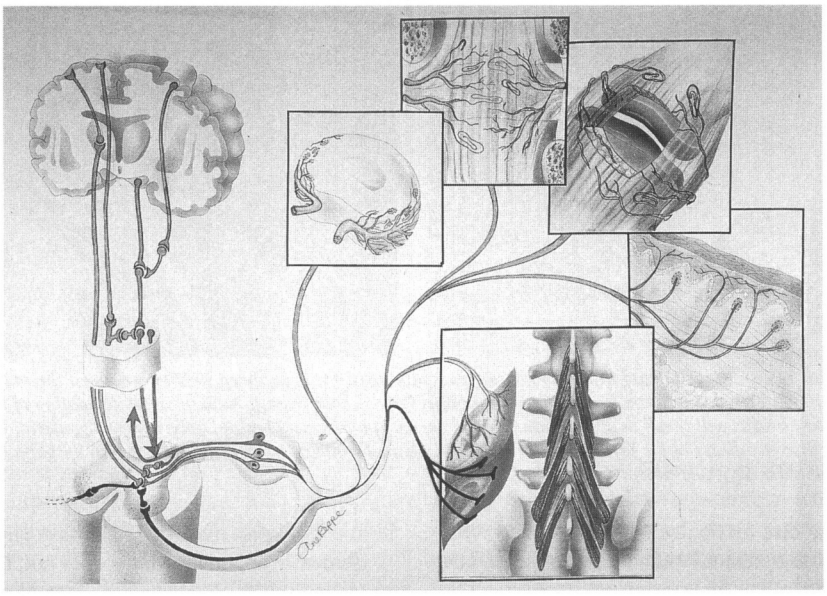

Figure 3. Functional connections between various spinal structures e.g. intervertebral discs, zygapophysial joints and spinal muscles may be clinically relevant in spinal disorders (Courtesy of Dr. Aage Indahl, Ostfold Central Hospital Spine Center, Fredrikstad, Norway).

exhibit nociceptors which could be involved in some forms of low-back pain, e.g. through mechanical or chemical/inflammatory influences in these tissues. Mechanoreceptor endings in facet joint tissues (McLain 1994, McLain and Pickar 1998) may also be important in normal and pathologically altered spinal function.

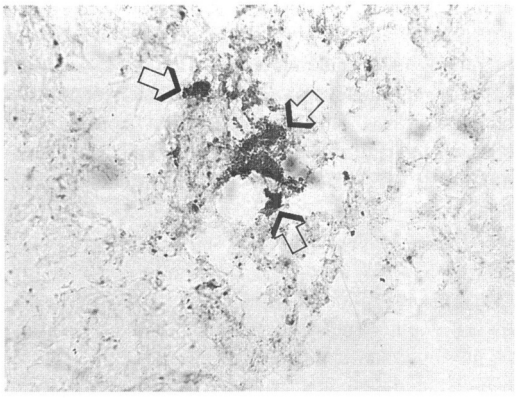

Figure 4. Spinal degenerative disease and sciatica may be linked to thromboses of small blood vessels within and in the vicinity of symptomatic nerve roots as was first shown by Jayson in 1992. With an antibody to activated platelets such tromboses are evident (arrows) in the periradicular tissue surrounding a symptomatic nerve root (Courtesy of Dr. Aklilu Habtemariam, Spine Research Unit research group, Helsinki, Finland).

Another interesting aspect of low-back pain pathophysiology relates to the nutrition of structures such as intervertebral discs and nerve roots (Yoshizawa et al. 1991) and to "clogged-up" blood vessels. Recent studies by Kauppila (Kauppila and Tallroth 1993) have shown an interesting correlation between low-back pain and atherosclerosis of feeding arteries from the aorta that has been verified by either pathological dissection or angiography. Studies by Jayson (1992) have revealed dilated periradicular veins with fibrin deposition and intraneural thromboses in patients with spinal degenerative disease. Such blood clots may also be visualized around symptomatic nerve roots when an antibody to activated platelets is employed (Fig. 4). What happens to e.g. epidural veins when "irritative" herniated disc tissue is expelled into this area near the nerve root has not yet been explored. The response to disc material of small nerves and sensory nerve endings, which have been demonstrated in the periradicular area (Grönblad and Virri 1997), will also require further study.

Future perspectives

Stopping and reverting damage, tissue engineering

Before damage can be stopped, a thorough knowledge of pathophysiology, the mechanisms producing the damage, must be at hand. Intervertebral disc degeneration and the pain resulting from it may be very

difficult to treat or revert, since 1) much of it may be genetically determined and 2) mechanisms producing such degeneration of intervertebral disc tissue may be complicated, involving a plethora of bioactive substances (Table). There may, however, be some key substance that has a pivotal function and which could be blocked/inhibited or perhaps even stimulated. Genetic engineering, if producing a long-term effect, may solve some of these problems. Such manipulation of pathological cell function may also reveal hitherto undiscovered aspects of pathophysiology.

Other very promising avenues of research seek to understand: 1) effects of intervertebral disc nucleus pulposus tissue on nerve root structure and function, and 2) mechanisms whereby displaced disc tissue will regress. Both areas of research will most probably, through a more detailed knowledge of pathophysiology, produce new methods for treating sciatica. It may in the future be possible to inject substances in target areas, which decrease the deleterious effects of displaced disc tissue on the nerve root and the dorsal root ganglion. It may also be possible to avoid more extensive operative intervention, by a more targeted "treatment" of the displaced tissue only, e.g. the injection of substance(s) that increase the rate of regression of displaced disc tissue (Haro et al. 1997a,b; Kobayashi et al. 1997) (Fig. 5). A better knowledge of the pathophysiology of the dorsal root ganglion, "the brain of the spinal motion segment" (Weinstein et al. 1988), in sciatica will also be of great importance in this respect.

Finally a few words about genetics. Are some of us more predestined than others to suffer from back pain? Or do some of us get more severe disc degeneration than others, even when trying to avoid all the possible risk factors for back pain and/or disc degeneration? At least disc degeneration as visualized by MRI, appears to be explained by primarily genetic influences (Battie et al. 1995). Suggesting new avenues of treatment recent in vitro experiments on disc cells isolated from human disc prolapse tissue have revealed a new possibility to transfer genes into intervertebral disc cells, thereby producing genetically modified cells, i.e. cells that produce "what they should" (Reinecke et al. 1997). Particularly cytokine genes and their inhibitors offer the potential to treat degenerative and inflammatory conditions (Reinecke et al.1997, Wehling et al. 1997). Despite the fate of many of us, already coded in our genetic constitution, to develop disc degeneration, genetic engineering may perhaps offer us help in the future. So instead of taking drugs to defeat the pain that is the consequence of aberrant disc function and biochemical pathology, there may be the possibility to treat the underlying disorder.

There is also great promise in recent animal experiments on osteoinduction of spinal fusion utilizing bone morphogenetic protein (BMP) (Boden et al.1995). More recently a study of osteoblast-related gene expression following soaking of the autograft with recombinant BMP-2 revealed an interesting time sequence and spatial pattern for the expression of the various BMP mRNA:s, which the investigators hope will provide a tool for gene-specific biologic strategies for enhancing spinal fusion healing (Boden et al, unpublished observations).

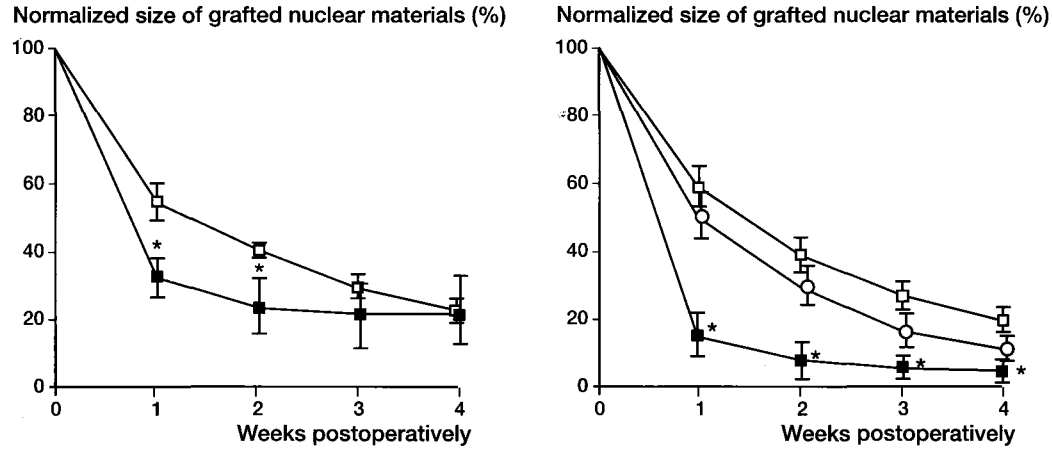

*Figure 5. In the near future it may be possible to speed up the regression of extruded disc tissue, through the specific injection of biological substances, such as e.g. (left) stromelysin-1 (■) or (right) monocyte chemoattractant protein 1 (rh MCP-1 single dose ○; daily administration ■) that work through biologically different mechanisms, but which both have been shown to speed up the regression of grafted nucleus pulposus material in animal experiments (control □; * $p < 0.05$) (Courtesy of Dr. Hirotaka Haro, Department of Orthopaedics and Rehabilitation, Vanderbilt University Medical Center, Nashville, TN).*

Specific goals, bullet areas for the next decade

A number of very interesting observations, many of them emanating from quite recent research findings, seem to hold promise for a very exciting arena of spinal basic science research in the next decade. The ultimate goals will be increased acuity in diagnosis and more specific non-operative treatment of spinal disorders and low-back pain. There will also be developments in the area of operative treatment, e.g. through improved spinal fusion methods based upon a thorough knowledge of mechanisms of osteoinduction.

Some possible bullet areas for research during the next decade would be:

- A deeper understanding of the mechanisms of sciatica, particularly with respect to cellular and molecular mechanisms that are set in motion when intervertebral disc tissue and nerve root (or dorsal root ganglion) become juxtaposed. The objective of this research will be new approaches for treating sciatica and this line of research will also most probably produce improvements in diagnostics.
- Another area of research relates to the mechanisms for low-back pain originating in the intervertebral disc. It is e.g. uncertain, at a population level, how often low-back pain is due to alterations in intervertebral discs and how often other causes should be sought for. The pathophysiological link between isolated anulus injury and severe degeneration of entire intervertebral discs should also be examined more closely.
- A third bullet area of research relates to interactions between various spinal tissues and components, e.g. the intervertebral disc or facet joint and spinal muscles, the way these interactions are altered in various spinal pathologies, and their role in everyday clinical practice .
- Promise may lie in the research that attempts to develop methods for improving the healing of pathologically altered spinal tissues. In this area of research, molecular biology and gene technology techniques should be developed further.

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