

## Biochemical injection treatment for discogenic low back pain: a pilot study

Robert G. Klein, MD<sup>a,\*</sup>, Björn C.J. Eek, MD<sup>a</sup>, Conor W. O'Neill, MD<sup>b</sup>, Caren Elin, DC<sup>c</sup>,  
Vert Mooney, MD<sup>d</sup>, Richard R. Derby, MD<sup>b</sup>

<sup>a</sup>Orthopedic Medicine, 2927 De La Vina, Suite D, Santa Barbara, CA 93105, USA

<sup>b</sup>Spinal Diagnostics and Treatment Center, 901 Campus Drive, Suite 310, Dale City, CA 94015, USA

<sup>c</sup>Comprehensive Musculoskeletal Care Center, 620 Augusta St., Box 516, Los Alamos, CA 93440, USA

<sup>d</sup>US Spine and Sport, 3444 Kearney Villa Road, Suite 205, San Diego, CA 92123, USA

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### Abstract

**Background context:** Biochemical treatment options including attempts at intervertebral disc restoration are desirable for the physiologic treatment of degenerative disc disease.

**Purpose:** This was a pilot study to test the potential effectiveness of intradiscal injection therapy using agents known to induce proteoglycan synthesis in the treatment of intervertebral disc disease.

**Study design:** Prospective, within subject, experimental design was applied in the study.

**Patient sample:** Thirty patients, average age 46.5 years, with chronic intractable low back pain of 8.5 years average duration, took part in the study. All patients had lumbar discography with reproduction of pain.

**Outcome measures:** Pretreatment Roland-Morris disability scores and visual analogue scores were compared with 1-year follow-up posttest values of these scores.

**Methods:** Lumbar intervertebral discs were injected with a solution of glucosamine and chondroitin sulfate combined with hypertonic dextrose and dimethylsulfoxide (DMSO). Assessment of pain and disability was completed before treatment and an average of 12 months after the last treatment.

**Results:** Posttreatment Roland-Morris scores for the entire group of 30 patients of  $6.4 \pm .994$  were significantly ( $p < .001$ ) lower than pretreatment scores of  $12.0 \pm .92$  (mean  $\pm$  SE). The posttreatment visual analogue scores of  $3.00 \pm .44$  were also significantly less than the pretreatment of  $6.11 \pm .33$  (mean  $\pm$  SE). Although the results were statistically significant for the 30 patients as a whole, 17 of the 30 patients (57%) improved markedly with an average of 72% improvement in disability scores and 76% in visual analogue scores. The other 13 patients (43%) had little or no improvement. Patients who did poorly included those with failed spinal surgery, spinal stenosis and long-term disability. There were no complications or serious side effects, although postinjection pain was moderate to severe for 48 to 72 hours and required epidural steroids in five cases.

**Conclusions:** The results of this pilot study suggest that intradiscal injection therapy with glucosamine, chondroitin sulfate, hypertonic dextrose and DMSO warrants further evaluation with randomized controlled trials. © 2003 Elsevier Inc. All rights reserved.

### Keywords:

Low back pain; Intervertebral disc; Zygapophyseal joint; Injection; Glucosamine; Chondroitin sulfate; Dextrose; DMSO

Chronic low back pain represents a major burden to society and to the individuals afflicted with this common condition. Despite the existence of sophisticated diagnostic tools,

a specific diagnosis is often elusive, and the choice of appropriate treatment remains largely empiric. Pathology within the intervertebral disc and zygapophyseal joint plays a major role in nonspecific low back pain syndromes [1–5]. The treatment of the intervertebral disc portion of the pain is difficult and controversial, and many patients with chronic intractable pain ultimately require lumbar fusion surgery after the failure of conservative treatments.

The intervertebral disc is a complex anatomic and biochemical structure composed primarily of fibrocytes and

FDA device/drug status: investigational/ not approved: glucosamine-chondroitin sulfate-DMSO.

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\* Corresponding author. 2927 De La Vina, Suite D, Santa Barbara, CA 93105, USA. Tel.: (805) 569-3169; fax: (805) 569-5670.

E-mail address: RKlein42@aol.com (R.G. Klein)

chondrocytes in an avascular macromolecular matrix of collagen and proteoglycans [6]. The degenerative processes associated with injury and aging result in biochemical and morphological alterations of the disc. Morphological changes of dehydration, fissuring and tearing of the nucleus, annulus and end plates are associated with molecular changes of decreased diffusion, decreased cell viability, decreased proteoglycan synthesis and alterations in collagen distribution [6–9].

Oral glucosamine and chondroitin sulfate, which enhance proteoglycan synthesis, have been used in multiple clinical trials and have generally been found to be effective and safe in the treatment of osteoarthritis of peripheral joints [10–15]. There is evidence that glucosamine and chondroitin sulfate synergistically enhance the natural hypermetabolic repair response of chondrocytes and retard the enzymatic degradation of cartilage [16]. This encouraged us to explore their potential use in degenerative disc disease.

Because the blood supply to the intervertebral disc is poor, and oral glucosamine and oral chondroitin sulfate do not clearly benefit patients with low back pain [12], we elected to perform a pilot study using intradiscal injectable glucosamine and chondroitin sulfate combined with other agents (dimethylsulfoxide [DMSO] and hypertonic dextrose) in an attempt to promote a reparative response in the intervertebral disc.

## Methods

### *Patient selection and follow-up*

Thirty consecutive patients with chronic intractable low back pain and positive discography participated in this prospective pilot study. These were all adult patients with chronic low back pain who failed to respond or responded poorly to multiple previous methods of treatment, including physical therapy, multiple analgesics, injection therapy, laminectomies, fusions and intradiscal electrothermal annuloplasty (IDET) procedures and were being considered for additional surgical procedures. They were all recruited during the 2000 calendar year. All of them had positive discography at one or more lumbar levels as evidenced by concordant pain provocation combined with morphologic disc abnormalities. Twenty-four of the 30 patients had involvement of two or more discs. Seven of the 30 patients had previously received the IDET treatment to a single disc with varying but generally poor responses. Six of these seven received treatment to the same disc previously treated by IDET, and one patient received treatment to a different disc. Three patients had prior lumbar fusions at a single level and were symptomatic at additional levels, and an additional three patients had laminectomies with persistent pain. Four patients, two of whom had a prior lumbar fusion, were disabled and had been incapacitated for more than 1 year. Three patients were involved in worker's compensation claims. The current data represent a minimum of 12 months

and a maximum of 20 months of follow-up from the time of initiation of therapy.

### *Composition of injected solutions*

A compounding pharmacist using sterile technique and *United States Pharmacopeia*–grade pharmaceuticals prepared the solutions. The “disc solution” consisted of 0.5% chondroitin sulfate, 20% glucosamine hydrochloride, 12% DMSO and 2% Marcaine ([Bupivacaine] Abbott Laboratories, Chicago, Illinois). These concentrations were derived based on solubility and tolerance characteristics of the constituents. This was mixed with 33% nonionic contrast and 33% of 50% dextrose at the time of injection. A total of 1 to 2 cc of this solution was injected into each involved disc. If any leakage of contrast into the epidural space was noted, the injection was terminated. The “disc solution” without chondroitin was used to inject the zygapophyseal joints at all treated disc levels and was mixed with equal amounts of 50% dextrose before injection. The chondroitin was omitted from the zygapophyseal injections, because previous testing of this solution intra-articularly proved it to be highly irritating to some of the patients. The zygapophyseal joint injections were performed after fluoroscopic confirmation of correct needle placement using intra-articular contrast and were performed at the same levels as the disc injections.

### *Injection protocol*

In order to avoid discomfort to the patient, the first series of injections was performed at the time of diagnostic discography. An intradiscal injection of 1 to 2 cc was used at each involved disc level as determined by discography. This was combined with injection of the zygapophyseal joints at the painful disc level(s) with the modified solution mixture as previously described.

### *Other treatments*

Patients were allowed to continue their ongoing treatment protocols and pain medications as needed. Five patients required epidural injections of corticosteroids 1 to 3 weeks after receiving the intradiscal injections because of a significant flare-up of pain. One patient received oral corticosteroids for 1 week after an intradiscal injection. The use of the steroids significantly reduced the pain in all six cases in which they were used.

### *Informed consent and monitoring for toxicity*

The institutional review board of the Pain Management Institute of Santa Barbara reviewed and approved the protocol for the study. Informed consent was obtained from each patient and followed all the approved guidelines for experimental investigation. Patients were questioned regarding any adverse reactions to the treatment. No specific laboratory monitoring was performed.

### *Assessment of outcome*

The success of any treatment for low back pain must rest on the patient's subjective assessment of pain and disability.

We used a previously validated disability questionnaire designed by Roland, consisting of 24 questions pertaining to activities of daily living [17]. A score of 0 corresponded to no impact of low back pain on activities of daily living, and a score of 24 indicated an extreme level of dysfunction. Adding up the number of positive responses before treatment and comparing this with the posttreatment total determined the pre- and posttreatment disability score. A standard visual analogue pain scale (0 to 10) was used to determine the patient's subjective estimate of pain before and after treatment. Statistical analysis was performed using a paired two-sample *t* test for the difference between means.

## Results

A total of 20 women and 10 men entered the study. The average age was 46.5 years (range, 27 to 62) and the average duration of pain was 8.5 years (range, 1 to 20). The minimum duration of follow-up was 12 months (average, 13 months). The average number of treatments was 2.5 (range, 1 to 4), and the average number of discs treated was two (range, one to four). The results of the pre- and posttreatment subjective disability and visual analogue pain scores are shown in Table 1. There was a statistically significant improvement in disability and pain scores in the group as a whole with approximately a 50% improvement overall in both the pain and disability scores. The statistical significance of these findings were positive despite the fact that only 17 patients (57% of the entire group) improved a minimum of 50% in either disability (average improvement 72%) or visual analogue scores (average improvement 76%), whereas 13 patients failed to respond significantly. This suggests a dichotomy of response rather than a uniform or universal response to treatment.

The data shown in Table 2 represent individual scores for each patient. The first 17 patients listed had improvement in disability or visual analogue pain scores of a minimum of 50% and were considered good-excellent responders. The final 13 patients were considered poor responders.

### Complications and side effects

All 30 patients experienced varying degrees of postinjection pain. In most cases this could be controlled with oral analgesics and was limited to 72 hours of moderate to severe pain. One patient required a tapering dose of oral corticosteroids for 1 week after treatment, and five patients required epidural corticosteroids because of temporary

exacerbations of pain. All patients were treated prophylactically with antibiotics at the time of each intradiscal injection, and there were no instances of disc space infection or other serious complications. There were no instances of skin rashes, systemic reactions, hypotension or allergic reactions noted with any of the injections. One patient developed increased leg pains for 2 months after the procedure, which completely resolved.

### Nonresponders

There were a total of 13 patients who responded minimally with average improvements in visual analogue scores of 14% and disability scores of 8%. All four patients who were disabled for more than 1 year failed to respond. One nonresponding patient (JC) had fibromyalgia syndrome with generalized musculoskeletal symptoms and responded poorly to two intradiscal injection treatments. One patient (JR) who failed to respond had advanced three-level degenerative disc disease and spinal stenosis accompanied by bilateral straight leg raise limitation (resulting from induction of nonradicular back pain) to 30 degrees and marked limitation of all lumbar movements. He had failed to respond to a previous laminectomy and foraminotomy. Two patients, both of whom received previous IDET therapy (RH, GG), elected to have spinal fusions after 3 months of failure to improve after a single intradiscal injection treatment. Two patients with previous lumbar spinal fusions, tissue hypersensitivity to palpation and limitations of straight leg raising to 50 degrees or less bilaterally failed to respond. Leg elevation in these cases resulted in back pain only, without demonstrable nerve root irritation.

### Excellent and good response

Seventeen patients were judged to have a good or excellent response by virtue of an improvement in disability and/or visual analogue pain scores of at least 50%, as noted in Table 2. There was an average reduction in the disability score of 72% and an average reduction of the visual analogue pain score of 76% in these 17 patients. The response to treatment was gradual in all patients, but all responders had significant improvements after the first treatment, whereas nonresponders failed to show significant improvements with the first or subsequent treatments. Three of the seven patients with prior IDET procedures were in the excellent response group, and four were in the nonresponder group, although one of these (RH) was not treated at his previous L4–L5 IDET level because he refused a repeat discogram at this level and received only one treatment at L5–S1 where the discogram was positive.

Table 1  
Averaged scores in all 30 patients

	Pretreatment	Posttreatment	p Value
Disability score	12.0 ± .925	6.4 ± .994	<.001
Mean ± SE			
Visual analogue score	6.11 ± .332	3.00 ± .441	<.001
Mean ± SE			

## Discussion

This nonrandomized prospective pilot study using intradiscal injections of glucosamine and chondroitin sulfate combined with hypertonic dextrose and DMSO demon-

Table 2  
Data for each patient

Patient	Age	Sex	Years of pain	RM pretreatment	RM posttreatment	VA pretreatment	VA posttreatment	Number of treatments	Number of discs
LG	56	F	20	14	0	6.9	0	2	1
PC*	55	F	5	17	4	8	0	2	2
ME	40	F	15	17	0	10	0	3	2
RJ	56	M	1	19	1	6.2	0.2	3	3
MM†	38	F	11	16	6	7	3	4	2
KT†	51	F	5	20	14	7.5	3	4	2
CB	51	F	5	3	1	6.1	0	2	2
PT	41	M	5	7	3	4.5	2	3	2
ME†	51	F	8	7	2	4.3	2.5	4	2
JL	54	M	20	10	1	6	1	2	2
JP*	27	F	3	6	5	5.7	1.5	3	2
NB	58	F	5	15	2	3.5	0	2	2
CH	57	F	15	13	2	7.3	5	2	2
ML	38	F	2	9	6	7	3.2	3	2
CR	35	F	20	14	0	7.5	0.5	3	4
JM	58	F	15	8	1	2.3	0	3	2
DF	42	M	2	11	7	6.8	3.4	2	1
JR*	58	M	15	10	9	8.7	9	2	3
BK	49	F	10	7	7	4.6	5	3	2
BH	55	M	10	3	3	5.7	5	2	1
TR†‡	35	F	4	14	9	8.5	4.5	2	3
AD	52	F	10	4	4	3.4	3	3	2
KA*	25	F	7	16	13	5.5	2.9	3	2
JM*‡	38	M	6	20	20	6.3	6.5	2	3
GG†	51	F	5	13	13	3.3	3.3	1	1
JC	34	F	3	13	15	7.1	5	2	1
TH‡	43	M	5	19	13	5	3.5	2	2
MJ*‡	34	F	10	16	12	8.5	7	3	2
RM†	52	M	7	7	7	4	4	2	2
RH†	62	M	5	12	12	6.1	6.1	1	1

F = female; M = male; RM = Roland-Morris disability score; VA = visual analog pain score.

\*Patients with prior laminectomy or fusion.

†Patients with prior intradiscal electrothermal annuloplasty treatments.

‡Patients with chronic disability.

strated significant improvements in pain and function in a group of patients with discogenic pain. Small nonrandomized open studies such as this one cannot provide definitive evidence for the efficacy of any treatment, but these preliminary results in this difficult group of patients with chronic pain who had multilevel degenerative disc disease suggest that this approach is worthy of further investigation.

The present study had no control or comparison group; historical comparisons are not valid under these circumstances and must be considered speculative. However, the difficulty of successfully treating patients with chronic pain who have degenerative disc disease at one or more levels using other methods of treatment is well documented. Schofferman et al. [18] compared the success of 270-degree fusions with 360-degree fusions in 48 patients. Disability scores measured by the Oswestry method showed approximately a 34% improvement in both fusion groups. Pain scores were improved by 45% in the 360-degree group and 35% in the 270-degree fusion group at a mean follow-up of 35 months. The Volvo award study by Fritzell et al. [19], from the Swedish Lumbar Spine Study Group, followed pa-

tients with chronic pain of approximately 8 years duration who had been on sick leave for at least 1 year. The investigators used the visual analogue scale to measure pain and the Oswestry score for disability. Their results after 2 years demonstrated that back pain was reduced by 33%, and disability was reduced by 25% in the surgical group. Outcome studies were performed by Karasek with a 12-month follow-up of patients who had single-level disc involvement and were treated with the IDET procedure [20]. Sixty percent of Karasek's patients achieved at least a 50% reduction of their visual analogue pain scores.

Studies have emerged over the past decade documenting the safety and efficacy of glucosamine and chondroitin sulfate, which act as essential substrates and contribute to the biosynthesis of proteoglycans [10–16]. Proteoglycans and collagens constitute the two major classes of macromolecules in the nucleus pulposus, annulus fibrosus and hyaline cartilage end plate. Although cells are necessary to control the growth and repair of the disc, its mechanical function is determined largely by the properties of the extracellular matrix [21]. The proteoglycans consist of sulfated glycosami-

noglycan side chains of chondroitin and keratan sulfate and hyaluronate bound to a protein core. Glucosamine sulfate forms half of the disaccharide subunit of keratan sulfate and of hyaluronic acid, which forms the backbone of proteoglycans aggregates in the intervertebral disc and in articular cartilage. Chondroitin sulfate is one of the predominant glycosaminoglycans in articular cartilage as well as in the intervertebral disc [21].

We identified a group of patients with chronic low back pain of more than 8 years average duration in whom the intervertebral disc was the likely primary pain generator based on discography. These patients are commonly seen in every orthopedic practice and present major challenges of management. We included the most difficult and refractory cases, including patients with long-term disability, worker's compensation claims, failed IDET procedures and failed back surgery in this pilot study. We used intradiscal injections of glucosamine and chondroitin sulfate with the theoretical intention of enhancing proteoglycan synthesis. This was coupled with an attempt to induce growth factor release promoted by the use of hypertonic dextrose. Elevation of extracellular glucose to as little as .5% has been shown to increase levels of IGF-1 and IGF-2 in human mesangial cells [22], TGF- $\beta$ -1 in human mononuclear cells [23], bFGF in human gingival fibroblasts [24] and platelet-derived growth factor in human mesangial cells [25].

Research using growth factors has led to the repair of full-thickness cartilage lesions in small animals, and studies of the canine intervertebral disc suggest that growth factors may be useful in modulating the repair of the nucleus and transition zone [26,27]. A single injection of TGF- $\beta$  has been shown to induce 3 weeks of proteoglycans synthesis [28].

This suggests that continuous exposure to growth factors may not be necessary for healing of joints (or discs) to occur. DNA levels for growth factor production increase within hours after cellular exposure to elevated glucose concentrations [29]. There may be elevated levels of metalloproteinases and other degradative enzymes in degenerative disc disease and in established cases of osteoarthritis that may block the effect of a single growth factor. The potential combination of multiple agents and the release of multiple growth factors may be necessary to overcome this inhibition. Glucose in addition to increasing multiple growth factors has also been found to suppress potential disrepair factors, including such interleukins as IL-2, IL-6 and IL-10 [23]. The exposure of cells to hyperosmolar solutions with changes in osmolarity of as little as 50 mOsm activates kinases, which also may have an effect on growth factor regulation [30].

DMSO was added to the injected solution to enhance diffusion of the dextrose, glucosamine and chondroitin throughout the full extent of the disc. Studies in rabbits with degenerative disc disease indicate that DMSO is necessary to allow a methylene blue carrier to penetrate the full extent of the disc (V Mooney, MD, unpublished data, February 2001). It also appears to have potent free radical scavenging

properties that may be useful in the setting of chronic pain and tissue hypoxia [31]. DMSO is US Food and Drug Administration approved for treatment of interstitial cystitis and is available in pure form.

The patients who demonstrated significant reductions in pain in our study generally responded slowly to the intradiscal treatment, consistent with a biologic rather than an analgesic response. Patients who proved to be responders invariably had improvements in pain after only one treatment, whereas those who ultimately failed to respond showed no improvement after their first or subsequent treatments. Typically, 3 or more months were required to appreciate the full extent of improvement from each treatment. Despite the selection process, which insured the inclusion of only the most treatment-refractory patients with chronic pain, there was improvement that was statistically significant. Three of the six patients previously treated unsuccessfully with the IDET procedure subsequently responded favorably to the disc and apophyseal injections. The longest follow-up in our series is only 20 months, and we do not know the potential for relapse, which will require longer follow-up.

The sharp demarcation of results into positive responders in 17 patients and negative responders in 13 suggests that identification of the characteristics that separate these two groups would be valuable and would potentially allow for a greater response rate. Based on our initial experience, future studies would exclude patients with prior fusions or long-term disability, and we would exclude patients who demonstrate bilateral limitations of the straight leg raise test (resulting from back pain) to less than 50 degrees. We would also exclude patients who demonstrate extreme tissue hypersensitivity to palpation, which often corresponds with chemically sensitive discs with discographic induction of pain at less than 30 psi and/or alternatively may be a marker that reflects pain-focused behavior. These patients may become candidates for intradiscal injection treatment after initial radiofrequency treatments or corticosteroid injections render the disc less sensitive. Prophylactic epidural injections of corticosteroids may also be considered in future studies to diminish the postinjection flare-up of pain that occurred in most patients in our series and was severe enough in 6 of the 30 cases to require epidural or systemic corticosteroids.

The present pilot study was neither blinded nor randomized, and we cannot rule out a placebo effect as a major contributor to the improvement. The history of spine care is replete with numerous therapies that have been touted as "breakthroughs" or "miracle cures" that have subsequently been proven to be worthless upon rigorous subsequent investigation.

Based on the results of this pilot study, we will now proceed to organize a randomized controlled trial to rigorously assess the effectiveness of this approach. Based on our preliminary results, this treatment approach is feasible, appears to have a low profile of side effects and, pending confirmation by controlled studies, may have the potential to avoid

more costly surgical and other invasive procedures. It may also be useful in cases where the IDET or similar procedures has failed to achieve a satisfactory response.

We hypothesize that the reductions in pain and disability seen in this study are the result of favorable alterations in the biochemical milieu of the intervertebral disc and apophyseal joints, but we have no direct proof that this is the case, and further studies, including serial magnetic resonance imaging scans, are clearly needed to address this important question.

Based on clinical presentation and discography, the primary source of pain in the patients in our study was the disc pathology. However, we elected also to empirically treat the zygapophyseal joints at the affected disc levels. The relative contribution of the intervertebral disc and zygapophyseal joints to the total burden of chronic low back pain in individual patients is debatable. There are studies that suggest a causal relationship between disc degeneration and osteoarthritis in the facet joints, and in most cases the severity of the osteoarthritis correlates with the extent of disc degeneration [9]. Other studies suggest that in patients with chronic low back pain the combination of discogenic pain and zygapophyseal joint pain is uncommon, and that the concept of the three-joint complex may be pathologically correct but not clinically relevant in the majority of cases [5]. Because both the discs and facet joints were treated in all individuals, we cannot exclude the possibility that some patients responded in part, or even wholly, as a result of the facet injections. Future studies will need to address the relative importance of injecting each of these structures.

Ideally, each component of the injection solution should be tested independently to determine optimal combinations and concentrations, but this was not practical in a private practice setting and with a pilot study. A randomized double-blind placebo-controlled study would be desirable to test this injection approach, but this would prove difficult in view of the temporary pain induced after treatment in all cases, which would make blinding difficult. Additionally, the use of fluoroscopic X-rays in a placebo group could not be justified. However, a prospective controlled trial in which eligible patients are randomized to receive either intradiscal injection therapy with corticosteroids or with the solution used in our pilot study would be worthwhile and is being planned.

Diwan et al. [32] has recently reviewed the topic of intervertebral disc replacement therapy as well as the potential for disc regeneration using a variety of growth factors. The possible role of recombinant human osteogenic protein-1 (rhOP-1) is especially relevant in that it appears to stimulate the metabolism of the nucleus pulposus and the annulus fibrosus, suggesting its potential use in promoting synthesis and repair of matrix in degenerating discs. Ideally, specific growth factors, once they are isolated and tested, can be used to stimulate chondrocytes and fibroblasts to induce a healing response. Until these growth factors become available and are proven effective in future studies, the best op-

tion is to study the use of indirect stimulants that may promote connective tissue healing.

## Conclusions

Intradiscal injections of a glucosamine hydrochloride and chondroitin sulfate solution combined with dextrose and dimethylsulfoxide may be useful to reduce chronic pain and disability in patients with multilevel degenerative disc disease. The results of this pilot study indicate that controlled comparative studies need to be performed to establish the efficacy of this treatment.

## References

- [1] Mooney V. Presidential address to the International Society for the Study of the Lumbar Spine, Dallas, 1986. Where is the pain coming from? *Spine* 1987;12:754–9.
- [2] Olmarker K, Blomquist J, Stromberg J, Nannmark U, Thomsen P, Rydevik B. Inflammation properties of nucleus pulposus. *Spine* 1995;20:665–9.
- [3] McCarron RF, Wimpee MW, Hudkins PG, Laros GS. The inflammatory effect of nucleus pulposus. A possible element in the pathogenesis of low back pain. *Spine* 1987;12:760–4.
- [4] Vanharanta H, Guyer RD, Ohnmeiss DD, et al. Disc deterioration in low back syndromes. A prospective, multi-center CT/discography study. *Spine* 1988;13:1349–51.
- [5] Schwarzer, A, Aprill C, Derby R, et al. The relative contributions of the disc and zygapophyseal joint in chronic low back pain. *Spine* 1995;19:801–6.
- [6] Guiot BH, Fessler RG. Molecular biology of degenerative disc disease. *Neurosurgery* 2000;47(5):1034–40.
- [7] Buckwalter JA. Aging and degeneration of the human intervertebral disc. *Spine* 1995;20(11):1307–14.
- [8] Pearce RH, Grimmer BJ, Adams ME. Degeneration and the chemical composition of the human lumbar intervertebral disc. *J Orthop Res* 1987;5(2):198–205.[/1a]
- [9] Steven RL, Ryvar R, Robertson WR, O'Brien JP, Beard HK. Biological changes in the annulus fibrosis in patients with low back pain. *Spine* 1982;7(3):223–33.
- [10] Deal CL, Moskowitz RW. Nutraceuticals as therapeutic agents in osteoarthritis. The role of glucosamine, chondroitin sulfate, and collagen hydrolysate. *Rheum Dis Clin North Am* 1999;25 (2):379–95.
- [11] McAlindon TE, LaValley MP, Gulin JP, Felson DT. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. *JAMA* 2000 15;283(11):1469–75.
- [12] Phillipi AF, Leffler CT, Leffler SG, Mosure JDC, Kim PD. Glucosamine, chondroitin and manganese for degenerative joint disease of the knee or low back: a randomized, double-blind, placebo-controlled pilot study. *Military Med* 1999;164(2):85–91.
- [13] Leeb BF, Schweitzer H, Montag K, Smolen JS. A metaanalysis of chondroitin sulfate in the treatment of osteoarthritis. *J Rheumatol* 2000;27(1):205–11.
- [14] da Camara CC, Dowless GV. Glucosamine sulfate for osteoarthritis. *Ann Pharmacother* 1998;32(5):580–7.
- [15] Reginster JY, Deroisy R, Rovati LC, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. *Lancet* 2001;357:251–6.
- [16] Lippello L, Woodward J, Karpman R, Hammad TA. In vivo chondroprotection and metabolic synergy of glucosamine and chondroitin sulfate. *Clin Orthop Rel Res* 2000 Dec;(381):229–40.
- [17] Roland MR, Morris RM. A study of the natural history of back pain. *Spine* 1983;8:141–4.
- [18] Schofferman J, Slosar P, Reynolds J, Goldwithe N, Kestler M. A

- prospective randomized comparison of 270 degree fusions to 360 degree fusions (circumferential fusions). *Spine* 2001;26:E207–12.
- [19] Fritzell P, Hagg O, Wessberg P, Nordwall A. 2001 Volvo award in clinical studies: lumbar fusion versus nonsurgical treatment for chronic low back pain: a multicenter randomized controlled trial from the Swedish Lumbar Spine Group. *Spine* 2001;26(23):2521–32.
- [20] Karasek M, Bogduk N. Twelve month follow-up of a controlled trial of intradiscal thermal annuloplasty for back pain due to internal disc disruption. *Spine* 2000;20:2601–7.
- [21] McDevitt CA. Proteoglycans of the intervertebral disc. In: Ghosh P, editor. *The biology of the intervertebral disc*. Boca Raton, FL: CRC Press, 1988;152–70.
- [22] Pugliese G, Pricci F, Locuratolo N, et al. Increased activity of the insulin like growth factor system in mesangial cells cultured in high glucose concentrations. Relation to glucose enhanced extracellular matrix production. *Diabetologia*. 1996;39 (7):775–84.
- [23] Reinhold D, Ansorge S, Schleicher ED. Elevated glucose levels stimulate transforming growth factor-beta (TGF-beta1), suppress interleukin IL-2, IL-6 and IL-10 production and DNA synthesis in peripheral blood mononuclear cells. *Horm Metab Res* 1996;28(6):267–70.
- [24] Ohgi S, Johnson PW. Glucose modulates growth of gingival fibroblasts and periodontal ligament cells: correlation with expression of basic fibroblast growth factor. *J Periodontal Res* 1996;31(8):579–88.
- [25] DiPaolo S, Gesualdo I, Ranieri E, Grandaliano G, Schena FP. High glucose concentration induces the overexpression of transforming growth factor-beta through the activation of a platelet derive growth factor loop in human mesangial cells. *Am J Pathol* 1996;149(6):2095–106.
- [26] Wakitani S, Imoto K, Kimura T. Hepatocyte growth factor facilitates cartilage repair: full thickness articular cartilage defect studied in rabbit knees. *Acta Orthop Scand* 1997;68(5P):474–80.
- [27] Thompson JP, Oegema TR, Bradford DS. Stimulation of mature canine intervertebral disc by growth factors. *Spine* 1991;16(3):253–60.
- [28] Van Beuningen HM, Glansbeek HI, van der Kraan PM, van den Berg WB. Differential effects of local application of BMP-2 or TGF-beta on both articular cartilage composition and osteophyte formation. *Osteoarthritis Cartilage* 1998;6(5):306–17.
- [29] Oh JH, Ha H, Yu MR, Lee HB. Sequential effects of high glucose on mesangial cell transforming growth factor beta-1 and fibronectin synthesis. *Kidney Int* 1998;54(6):1872–8.
- [30] Okuda Y, Adroge HJ, Nakajima, et al. Increased production of PDGF by angiotensin and high glucose in human vascular endothelium. *Life Sci* 1996;59(17):1455–61.
- [31] Walker M. *DMSO: nature's healer*. Garden City Park, NY: Avery Publishing Group, 1993.
- [32] Diwan AD, Parvataneni HK, Khan SN, et al. Current concepts in intervertebral disc restoration. *Orth Clin North Am* 2000;31(3):453–63.



## Fifty-Five Years Ago in Spine . . .

In 1948, Carl Hirsch (1913–1973) published the results from use of discography for 16 patients with lumbar disc disease [1]. He found the study helpful, reported no complications and stated that

subsequent surgeries revealed no harm done to the discs by the procedures. Hirsch, who had trained at Karolinska and studied under Langenskiöld in Helsinki, Seddon and Trueta at Oxford and Joseph Barr in Boston, chaired orthopedic programs at Uppsala, Göteborg and Karolinska and made numerous contributions to spine research.

### References

- [1] Hirsch C. An attempt to diagnose the level of a disc lesion clinically by disc puncture. *Acta Orthop Scand* 1948;18:132–40.