CHAPTER 2

THE ORIGIN OF LOW BACK PAIN

The International Association for the Study of Pain (IASP) has defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage".[50] This rather broad description implicates both sensory and emotional factors to be involved in the pain experience. The sensory part refers to the signal system of nociception, activated when adequate stimuli provoke free nerve endings to transmit signals to the spinal cord or brain stem to finally become aware in the brain. The emotional part is a complex signal system with cognitive, emotional, and behavioral components and occurring subsequent to nociceptive stimulation.[23] Actual and potential tissue damage refers to the fact that pain can occur in the absence of tissue damage and therefore is not invariably linked-up with a damaging stimulus. In assessing the problem, Loeser[48] subdivides four modalities:

Nociception: potentially tissue-damaging thermal, chemical, electrical or mechanical energy impinging upon specialized nerve endings that in turn activate A-delta and C fibers.

Pain: nociceptive input to the nervous system and its awareness.

Suffering: negative affective response generated in higher nervous centers by pain and other situations: loss of loved objects, stress, anxiety, etc.

Pain behaviour: all forms of behaviour generated by the individual commonly understood to reflect the presence of nociception, including speech, facial expression, posture, seeking health care attention, taking medications, refusing to work.

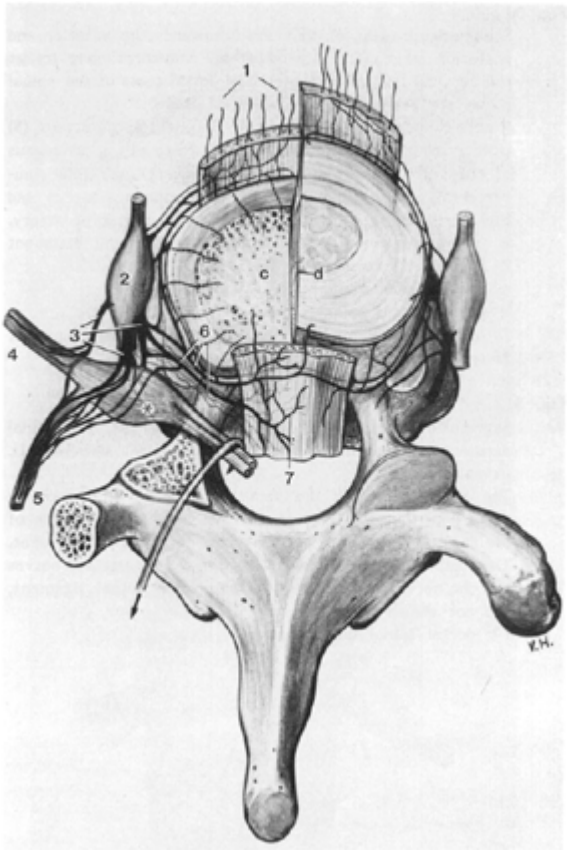
When an attending physician is confronted with a patient suffering from low back pain a combination of anatomical, physiological, and psychosocial factors underlies the patient's pain experience. To what extent each of these components attribute to the pain experience must be evaluated in the individual with regard to diagnosis making and treatment of choice. In patients with a predominant physical source of the low back pain, additional medical investigations and physical treatment are appropriate. In depressed patients with apparent psychosocial difficulties, psychotherapeutic and social intervention is rather indicated. In the latter category, excessive medical and surgical treatments will be irrelevant and are potentially hazardous.

In order to understand the very nature of low back pain, various neuroanatomical mechanisms of the lumbar pain will be discussed in 2.1. Low back pain as a result of spinal degeneration will be discussed in 2.2.

2.1 NEUROANATOMICAL CONSIDERATIONS IN LOW BACK PAIN

2.1.1 Innervated structures

In principle, any structure in the lumbar spine that posesses a nerve supply can become a source of pain when affected by pain-producing tissue damage.[7] Therefore the possible sources of pain can be determined by reviewing the innervated structures and the lesions that might affect them. Several authors, including Bogduk[8,11,12], Edgar[19], Groen[31-33] and Hirsch[38], have described the innervation of the vertebral column and its associated structures. Innervated structures of the lumbar spine are the vertebral venous plexuses and the dura mater, the zygapophysial joints, the ligaments of the vertebral arches, the back muscles and their fascia, the vertebral bodies and their covering periosteum, the vertebral laminae, the longitudinal ligaments and the discs (see figure 2.1). Possible pain mechanisms are shown in figure 2.2.[67]



1) nerve plexus of the anterior longitudinal ligament
2) sympathic trunk
3) rami communicantes
4) ventral ramus spinal nerve
5) dorsal ramus spinal nerve
6) sinuvertebral nerves
7) nerve plexus of the posterior longitudinal ligament

c) vertebral body
d) intervertebral disc

Figure 2.1 Schematic drawing of the innervation of the upper lumbar spine according to Groen.[32] (printed with permission)

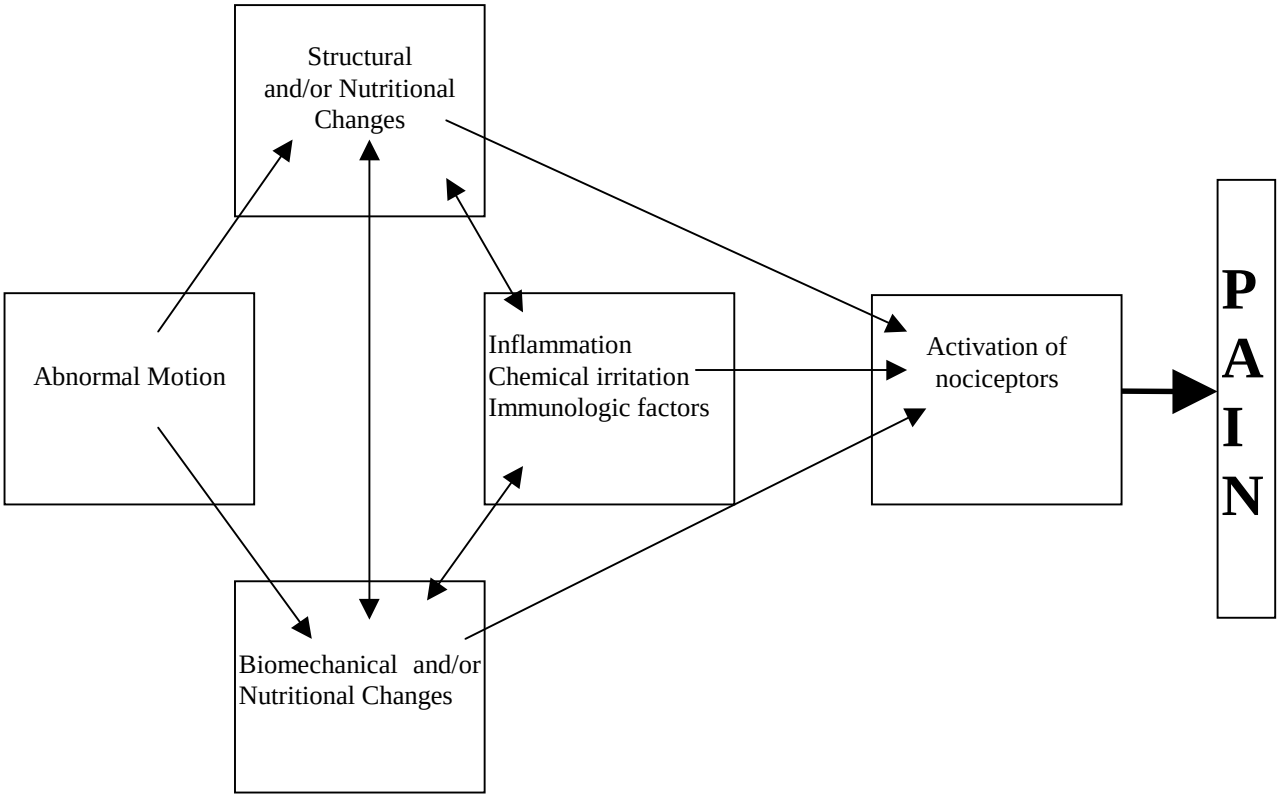


Figure 2.2 Possible mechanisms of low back pain.

Bogduk[7] has reviewed the various lesions of the lumbar spine that might be responsible for low back pain. Of the innervated structures of the lumbar spine, the venous plexuses are not thought to play a role in the onset of acute low back pain. The dura mater may undoubtly be a source of acute low back pain when irritated by pus (meningitis), blood (subarachnoid hemorrhage) or reactive exudates (disc herniation). No lesions of the ligamentum flavum, the interspinous, the supraspinous or the iliolumbar ligaments are likely to cause low back pain. Like every muscle in the body, any of the individual back muscles could become a source of pain following excessive exertion or sudden unexpected stretch. These selflimiting conditions possibly explain a large proportion of the selflimiting acute back pain cases.

Well known sources of low back pain are fractures, infections or expanding lesions of the vertebral bodies and other bony elements of the lumbar spine. Subchondral fractures and fractures of the articular-processes may also affect the lumbar zygapophyseal joints in such a way that they become a source of pain. Theoretically, the zygapophyseal joint may also become painful following trauma, when damaged meniscoid structures act as loose bodies within the joint, or become trapped in the subcapsular pockets of the joints. Then,

the innervated meniscoid structures are painful themselves[27] or elicit pain by stretching the joint capsule.
According to Bogduk and Jull[9,10], this zygapophyseal meniscus entrapment theory is also applicable to the relatively common clinical syndrome of "acute locked back". In this condition the patient, having bent forward, is unable to straighten because of severe focal pain on attempted extension. Until now its cause remains speculative. We firmly believe, however, that a more valid explanation of the "acute locked back", "Hexenschuss" or "witch's blow" is damage to the intervertebral disc. Physical stress related strains of the anulus fibrosus are one of the most potent, yet overlooked, sources of acute low back pain[7]. The anular strains can be peripherally (rim lesions), circumferentially (concentric) or radially. Since the anulus fibrosus is densely innervated it is not surprising that these ruptures are painful.[7,52,54] Secondary to painful movement muscle spasms may occur resulting in an "acute locked back". Tears may be produced in the anulus following twisting or flexion-rotation injuries or as a result of excessive compression. The possibility of developing these tears is increased when the vertebra is flexed and when the disc is submitted to lateral stress. The collagen fibers will then become subjected to microtrauma, a process often seen in disc degeneration (see 2.2 spinal degeneration and low back pain). It is interestingly that torsion injury inflicts lesions in the anulus fibrosus while the nucleus pulposus virtually remains unaffected.[22]

2.1.2 The pain pathway

The free nerve endings of the innervated structures, also called nociceptors (Latin nocere = to injure), respond selectively to damaging stimuli. An action potential is then generated which passes along the pain fibers into the dorsal horn of the spinal cord where it synapses for the first time. The second order neuron conducts the action potential across the spinal cord and synapses in the white matter of the anterolateral spinothalamic tract to the thalamus. Other ascending pain pathways are the spinoreticular tract, spinomesenchephalic tract, spinocervical tract, and the dorsal column.[43] The third order neuron sends the message to the somatosensory cortex of the brain. In addition to the ascending tracts there are also descending inhibitory circuits in the spinal cord and local excitatory and inhibitory circuits in the dorsal horn.

Nociceptors
In humans, pain is mediated by the several different nociceptors:

1. Mechanical nociceptors, which are activated only by strong mechanical stimulation and most effectively by, sharp objects. A pinprick or pinch causes a brisk response while no response is evoked when a blunt probe is pressed firmly into the skin.

2. Thermal nociceptors which respond when the receptive field is heated to temperatures greater than 45 °C, the heat pain threshold in humans.

3. Polymodal nociceptors which respond equally to all kinds of high-intensity noxious stimuli; mechanical, electrical, heat and chemical.

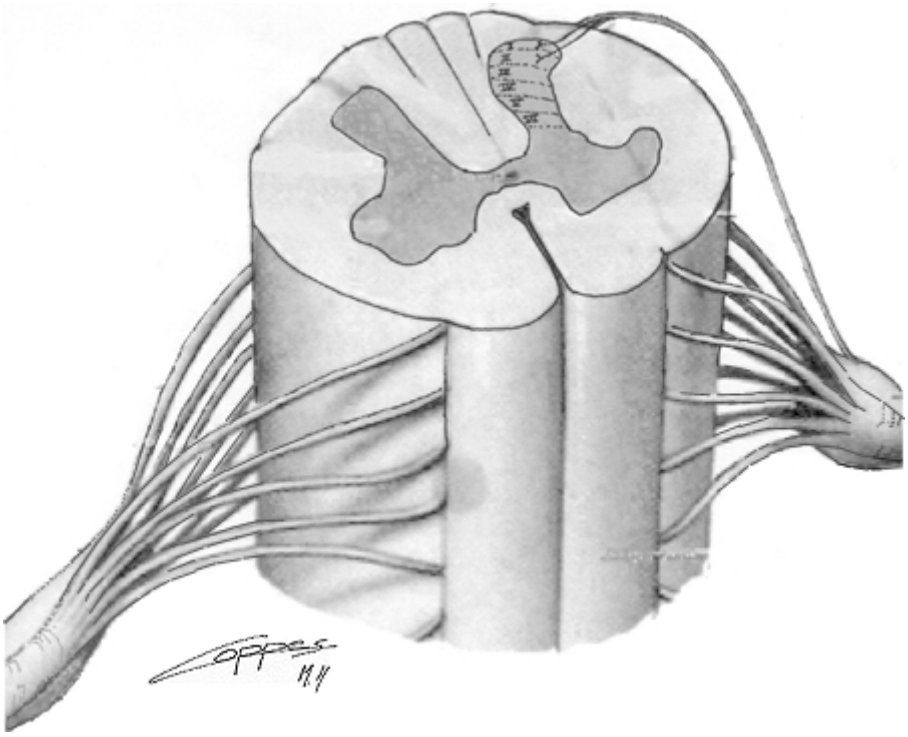
The noxious stimulus activates the nociceptor by depolarizing the membrane of the sensory ending, but the exact mechanisms by which the diverse stimuli depolarize the nerve endings and trigger an action potential are not known.[43] The nociceptors can be activated and sensitized by agents resulting from tissue damage such as potassium, serotonin, bradykinin, histamine, prostaglandins, and leukotrienes. The sensation of pain may be enhanced, also called hyperalgesia, and this may involve a lowering of the threshold of the nociceptors or an increase in the magnitude of the pain evoked by suprathreshold stimuli. The nociceptors themselves can also release peptides, such as substance P, thus sensitizing the nerve endings.

Nerve fibers

The nerve fibers responsible for pain sensation are the A-delta (Aδ) and C fibers.[34,49] The Aδ fibers are thinly myelinated and conduct at about 5-30 m/s. Activation of these fibers causes a sharp, pricking pain. The free nerve endings include thermal and mechanical nociceptors. The small diameter, unmyelinated C fibers conduct a sickening burning sensation following fast pain at 0.5-2 m/s. The Aδ and C fibers are not solely pain fibers, but are also involved in sensing temperature, pressure, and crude touch. The free nerve endings include the polymodal nociceptors.

The synapses of nociceptive fibers with dorsal horn neurons

The cell bodies of the Aδ and C fibers are located within the dorsal root ganglion. The myelinated Aδ fibers predominantly terminate on projection neurons in the most superficial layer (lamina I) of the dorsal horn[43], also known as the marginal zone; some fibers project more deeply (figure 2.3). The substantia gelatinosa (lamina II) contains the terminals of the unmyelinated, polymodal nociceptive C fibers. By means of stalk cell interneurons in lamina II the unmyelinated C fibers may contact the projection neurons in lamina I.



I - lamina 1
II - lamina 2
III - lamina 3
IV - lamina 4
V - lamina 5
VI - lamina 6

Figure 2.3 Synapses of nociceptive fibers in dorsal horn of myelum (laminae according to Rexed[59]).

In the dorsal horn, chemical transmitters transmit the nociceptive signals. The Aδ and C fibers release transmitters which can evoke fast and slow postsynaptic potentials in the superficial dorsal horn neurons. Neuropeptides that can be produced by the afferent neurons include substance P, somatostatin, cholecystokinin-like substance, vasoactive intestinal polypeptide, calcitonin gene-related peptide, gastrin-releasing peptide, dynorphin, enkephalin, and galanin.[42,66]

Of all these transmitters substance P has been studied most extensively. In 1931,Von Euler and Gaddum[20] discovered the polypeptide substance P (SP). Identification of its structure by Leeman et al.[18] facilitated important progress in SP research. SP an eleven-amino acid neuropeptide produced within the dorsal root ganglion in cell bodies of primary afferent neurons and that is delivered to the central and peripheral parts of the neurons by axonal transport.[66] At the peripheral nerve ending SP causes vasodilatation, plasma extravasation, and release of histamine from mast cells (figure 2.4).

Thus, when tissue damage occurs, substances like bradykinin and prostaglandins are released which in turn activate the nociceptors. Activation of the nociceptors results in release of neuropeptides, such as SP, producing histamine release, vasodilatation and plasma extravasation. Histamine excites the nociceptors directly and the vascular changes result in edema causing further liberation of bradykinin.[57]

SP released in the first synapse evokes a slow excitatory postsynaptic potential (EPSP) in dorsal horn cells. It must be noted that the role of SP as a pain transmitter is only one of many physiological roles of SP.[55] Furthermore, SP is present in only 10-20% of primary afferent fibers. The C- and Aδ fibers use various excitatory and possibly inhibitory transmitters. Discovery of these transmitters and their antagonists may open up new possibilities for the development of new non-narcotic analgesics.

Figure 2.4 Activation and sensitization of nociceptors, transduction along the pain fibers and their termination on projection neurons in the dorsal horn of the spinal cord.[66]

Pain perception

There are five major ascending pathways that carry the nociceptive information from the projection neurons of the dorsal horn to the brain: the spinothalamic tract, the spinoreticular tract, the spinomesenchephalic tract, the spinocervical tract, and the dorsal column of the spinal cord. The spinothalamic tract is the most prominent ascending pathway originating from the neurons in laminae I, IV and V of the dorsal horn and terminating in the thalamus. The information is then sent to the post-central gyrus of the brain where the pain is localized and interpreted. The frontal and temporal lobes provide Affective and memory components.

Central mechanisms that modulate pain

The spinal cord also contains descending pathways arising from several structures in the brain (hypothalamus, periaqueductal grey matter of the midbrain, locus ceruleus, ventromedial, and ventrolateral medulla) which can inhibit the nociceptive projection neurons of the dorsal horn by releasing neurotransmitters that act both pre- and post-synaptically.[61] A second way to inhibit nociceptive transmission is by endogenous opioid peptides (enkephalins, endorphins, dynorphins) whose receptors are located at key points in the pain modulating system.

2.2 SPINAL DEGENERATION AND LOW BACK PAIN

Spinal degeneration is a normal part of the aging process but unfortunately it may be the cause of low back symptoms as well. Degenerative changes affect all structures of the motion segment, including the intervertebral discs, facet joints, and ligaments.[24] The

spinal degeneration process is initiated in the intervertebral disc resulting in secondary changes in the facet joints and ligaments because of load shifts from the disc to these structures (see figure 2.5). This concept is supported by many studies on disc degeneration.[14,16,29,56,65] Only in exceptional cases facet degeneration can occur without preceeding signs of disc degeneration.[64] In addition it has been reported that facet joint pathology may accelerate the degenerative process of the disc.[17,51,62]

The progress of spinal degeneration can be divided into three phases as suggested by Kirkaldy-Willis.[45] In stage I (dysfunction), changes in biochemical composition, physiology, and biomechanics of the motion segment may result in clinical symptoms. When these changes result in increased mobility at the affected level and cause symptomatic instability it is called phase II (instability). In phase III (stabilization), the motion segment will stabilize because of biochemical alterations and spinal osteophyte formation. In this last phase symptoms may subside or symptoms of spinal stenosis may occur due to osteophyte formation and facet hypertrophy. The biochemical, physiological, and biomechanical changes in the three phases of spinal degeneration are apparently equal in both the normal aging process and in the symptomatic degenerative lesions. With the exception of severe, multiple degenerative disease, there is no correlation between the degenerative process shown on radiographs and the incidence or severity of low back pain.[25,47] It is not understood why these changes generally do not correlate with the patient's symptoms. For a better insight in the relation between degeneration of the lumbar spine and low back pain, the degenerative changes of different elements of the motion segment will be discussed below.

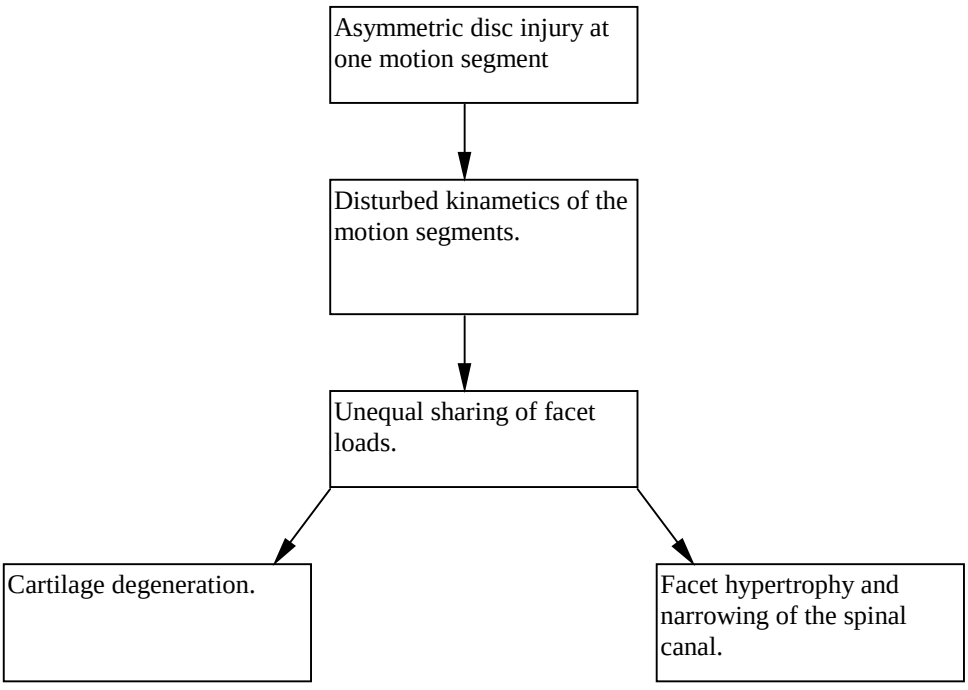


Figure 2.5 Consecutive steps of degeneration of the motion segment.

Degenerative changes of the intervertebral disc

Fundamental changes occur in the intervertebral discs during degeneration and aging. Biochemical changes in the nucleus pulposus include decrease in the proteoglycan concentration[4,30,36] and water content[39], and an increase in collagen[39] and collagen-proteoglycan binding.[1] In early adult life, the proteoglycans make up about 65% of the dry weight of the nucleus but this decreases to about 30% at the age of 60.[4] The proteoglycans also become smaller, lighter in molecular weight, and their composition changes.[21] The water content of the nucleus changes from about 88% at birth to about 65-70% at the age of 75.[30] The collagen content and the collagen binding of the nucleus pulposus increases and the fibril diameter of the collagen increase as well. [3,53] The collagen type II of the nucleus starts to resemble the type I collagen of the anulus fibrosus. In the anulus fibrosus, the collagen content also increases[15] but the average fibril diameter decreases.[37] The concentration of the elastic fibers in the anulus decreases from 13% at age 26 to 8% at age 62.[44]

With aging related degeneration, the intervertebral disc becomes progressively dry, stiff, and less resilient. It also becomes more difficult to distinguish the nucleus pulposus from the transitional zone since its specific features disappear with age. In the elderly, the disc appears as a solid plate of fibrocartilaginous tissue surrounded by the anulus fibrosus.[6,21,37,58] Since aging of the intervertebral disc and disc degeneration are continuous processes attempts have been made to develop grading systems for the study of disc degeneration based on disc morphology, discographic-features and magnetic resonance (MR) appearance.

When the nucleus becomes more fibrous and drier its ability to exert fluid pressure and to transmit weight weakens (see Ch 1: Clinical anatomy of the lumbar spine).[46,68] There will be less radial pressure being build up in the anulus fibrosus and the anulus will be subjected to greater vertical loads. The collagen lamellae also may become more fibrillated and in combination with the mechanical overload of the anulus it may give rise to cracks and fissures.[40] These lesions are believed to be the first step in the process of degeneration of the motion segment. The concomitant pain may in part be related to the chemical environment within the degenerated disc and the sensitized state of its anular and perhaps even nuclear nociceptors (see Ch 3). [66]

Degenerative changes of the facet joints

The degenerative changes of the facet joints are similar to osteoarthritis in other synovial joints.[24] Biochemically, quantitative and structural changes occur in the cartilage proteoglycan and collagen.[13,41,69,70] In continuation of structural degeneration of cartilage focal and diffuse erosions may occur with full thickness loss of cartilage as a result. In addition erosive changes of the cartilage may induce proliferation and increase of its matrix synthesis. The resulting osteochondrophytes produce sclerosis of subchondral bone and subchondral bone cyst formation. The degeneration process of the facet joints also includes biomechanical, inflammatory and immunological factors.[28]

Pain from an arthrotic facet joint may be provoked by free nociceptive nerve endings and mechanoreceptors abundantly present in the facet capsules.[8] They can be activated by inflammatory and immune responses or by mechanical factors.[66] Furthermore, in facet degeneration, a well known cause of pain radiating in one or both legs is compression of nerve roots in the lateral recess of the spinal canal due to hypertrofied joints or synovial cysts.

Degenerative changes of the ligaments

With increasing age ligamentous changes occur including disorganization of ligament fibrillar and cellular alignment, selective increase of collagen degradation over formation, and proteoglycan decrease associated with loss of water.[24] Pain symptoms may result from their contribution in spinal stenosis.[16]

Degenerative changes of the vertebral bodies and end-plates

With aging, the vertebral end-plate, originally part of the growth plate of the vertebral body, becomes thinner, its growth zone decreases and will contain less proliferating cells, and ossification will take place at the peripheral areas.[5] At the age of about twenty, the subchondral bone plate is formed which separates the vertebral end-plate from the vertebral body. Because of the subchondral bone formation and because of further ossification with aging and degeneration, the nutrition of the avascular disc progressively decreases which causes biochemical changes in the disc.[5]

The trabeculae in the vertebral body change in size and pattern with aging and degeneration, resulting in decreased vertebral body strength and density.[2,60,63] Characteristic is the loss of horizontal trabeculae, particularly in the central part of the vertebral body.[2,63] With the loss of vertebral body trabeculae, less of the compressive load is borne by the trabecular bone and much more by the cortical bone.[60,68] Consequently, the vertebral body becomes less resistant to deformation and injury.

The end-plates may, partly due to lacking support of the underlying bone[35], develop microfractures which can accelerate the degenerative process and contribute to the occurence of low back pain.[24] Fractures of the end-plate may extend to a degree that allows nuclear material to extrude into the vertebral body, a fenomenon known as Schmorl's nodes. These end-plate infractions occur with equal frequency in patients with and without a history of low back pain so the importance of Schmorl's nodes in the cascade of factors causing low back pain remains unsolved.[26]

2.3 SUMMARY

Low back pain is a complex entity of nociception, pain conduction, pain perception, and pain modulation greatly affected by emotional factors. Any innervated structure of the lumbar motion segment is a potential source of pain. Generally recognized sources are the zygapophyseal joints, the para-vertebral muscles, the dura mater, the anterior and posterior longitudinal ligaments, and the intervertebral discs. Pain arising from these musculoskeletal structures of the lumbar spine is described as "typical" low back pain. Pain arising from disorders of the spinal nerves and spinal nerve roots is called "radicular pain" or "sciatica".

A variety of lesions can cause low back pain, but of particular interest is low back pain as a result of spinal degeneration. Spinal degeneration is a sequence of biochemical, biomechanical, and physiological changes, starting in the intervertebral disc and finally affecting all structures of the motion segment. Spinal degeneration affects everyone since it is a normal part of the aging process. Interestingly, some people will develop low back pain symptoms as a result of the degeneration process and some do not. So far, it has been hard to differentiate between symptomatic spinal degeneration and normal physiologic aging events, but some insight in the underlying mechanisms has been gained yet.

REFERENCES

1. Adams P, Muir H. Qualitative changes with age of human lumbar discs. Ann Rheum Dis 1976;35:289-296.
2. Atkinson PJ. Variations in trabecular structure of vertebrae with age. Calcif Tissue Res 1967;1:24-32.
3. Baily AJ, Herbert CM, Jayson MIV. Collagen of the intervertebral disc. Ch 12 In: Jayson MIV, ed. The Lumbar Spine and Backache. New York: Grune & Stratton, 1976.
4. Beard HK, Stevens RL. Biochemical changes in the intervertebral disc. Ch 14 In: Jayson MIV, ed. The Lumbar Spine and Backache, Second Edition. London: Pitman, 1980.
5. Bernick S, Cailliet R. Vertebral end-plate changes with aging of human vertebrae. Spine 1982;7:97-102.
6. Bijlsma F, Peereboom JWC. The aging pattern of human intervertebral discs. Fluorescent substance and amino acids in the anulus fibrosis. Gerontologia 1972;18:157-168.
7. Bogduk N. Acute back pain - What is the lesion? Proceedings of a symposium on Acute Back Pain, 2nd European Congress on back pain. Montreux 1988:6-16.
8. Bogduk N. The innervation of the lumbar spine. Spine 1983;8:286-293.
9. Bogduk N, Engel R. The menisci of the lumbar zygapophyseal joints. A review of their anatomy and clinical significance. Spine 1984;9:454-460.
10. Bogduk N, Jull G. The theoretical pathology of acute locked back: a basis for manipulative therapy. Man Med 1985;1:78-82.
11. Bogduk N, Tynan W, Wilson AS. The nerve supply to the lumbar intervertebral discs. J Anat 1981;132:39-56.

12.Bogduk N, Wilson AS, Tynan W. The human lumbar dorsal rami. J Anat 1982;134:383-397.
13.Bollet AJ, Nance JL. Biochemical findings in normal and osteoarthritic articular cartilage. II. Chondoitin sulphate concentration and chain lenght, water, and ash content. J Clin Invest 1966;44:1170-1177.
14.Bradford DS, Oegema TR Jr, Cooper KM, et al. Chymopapain, chemonucleolysis, and nucleus pulposus regeneration: A biochemical and biomechanical study. Spine 1984;9:135-147.
15.Brickley-Parsons D, Glimcher MJ. Is the chemistry of collagen in intervertebral discs an expression of Wolff's law? A study of the human lumbar spine. Spine 1984;9:148-163.
16.Bywaters EGL. The pathological anatomy of idiopathic low back pain. Ch 10 In: White AA III, Gordon SL, eds. American Academy of Orthopaedic Surgeons Symposium on Idiopathic Low Back Pain, St. Louis: Mosby, 1982.
17.Cauchoix J, Yaacubi E, Romero CG, et al. An experimental model of lumbar degenerated discs in rabbits. Presented at the Tenth Meeting of the International Society for the Study of the Lumbar Spine, Montreal, Canada, 1984.
18.Chang MM, Leeman SE, Niall HD. Amino-acid sequence of substance P. Nat New Biol 1971;232:86-87.
19.Edgar MA, Ghadially JA. Innervation of the lumbar spine. Clin Orthop 1976;115:35-41.
20.Euler US v, Gaddum JH. An unidentified depressor substance in certain tissue extracts J Physiol 1931;72:74-87.
21.Eyre D, Benya B, Buckwalter J, et al. Basic science perspectives. In: Frymoyer JW, Gordon SL, eds. New Perspectives on Low Back Pain. Park Ridge: American Academy of Orthopaedic Surgeons, 1989:133-214.
22.Farfan HF, Cossette JW, Robertson GH, Wells RV, Kraus H. The effects of torsion on the lumbar intervertebral joints: the role of torsion in the production of disc degeneration. J Bone Joint Surg (Am) 1970;52A:468-497.
23.Fordyce WE. What is Pain? In: Fordyce WE, ed. Back Pain in the Workplace: Management of Disability in Nonspecifc Conditions. Seattle: IASP Press, 1995:11-17.
24.Frymoyer JW, Moskowitz RW. Spinal degeneration. Pathogenesis and medical management. In: Frymoyer JW, ed. The Adult Spine: Principles and Practice. New York: Raven Press, 1991:611-636.
25.Frymoyer JW, Newberg A, Pope MH, et al. Spine radiographs in patients with low-back pain. An epidemiological study in men. J Bone Joint Surg 1984;66A:1048-1055.
26.Frymoyer JW, Newberg A, Pope MH, Wilder DG, Clements J, MacPherson B. Spine radiographs in patients with low back pain. An epidemiological study in men. J Bone Joint Surg (Am) 1984;66:1048-1055.
27.Giles LGF, Taylor JR, Cockson A. Human zygapophyseal joint synovial folds. Acta Anat 1986;126:110-114.
28.Goldenberg DL, Egan MS, Cohen AS. Inflammatory synovitis in degenerative joint disease. J Rheumat 1982;9:204-209.
29.Gotfried Y, Bradford DS, Oegema TR Jr. Facet joint changes after chemonucleolysis-induced disc space narrowing. Spine 1986;11:944-950.
30.Gower WE, Pedrini V. Age related variation in protein polysaccharides from human nucleus pulposus, annulus fibrosus, and costal cartilage. J Bone Joint Surg (Am) 1969;51A:1154-1162.

31.Groen GJ. Innervation of annulus fibrosis in low back pain (Letter). Lancet 1990;189-190.
32.Groen GJ. Contributions to the anatomy of the peripheral autonomic nervous system. Ph-D thesis, University of Amsterdam, 1986.
33.Groen GJ, Baljet B, Drukker J. Nerves and nerve plexuses of the human vertebral column. Am J Anat 1990;188;282-296.
34.Guyton AC. Sensory receptors and their basic mechanism of action. In: Guyton AC, ed. Textbook of Medical Physiology, 6th ed.. Philadelphia: Saunders Co., 1981:588-96.
35.Hansson T, Roos B. Microcalluses of the trabeculae in lumbar vertebrae and their relation to the bone mineral content. Spine 1981;6:375-380.
36.Happey F. A biophysical study of the human intervertebral discs. Ch 13 In: Jayson MIV, ed. The Lumbar Spine and Backache. New York: Grune & Stratton, 1976.
37.Happey F, Pearson CH, Naylor A, et al. The aging of the human lumbar intervertebral disc. Gerontologia 1969;15:174-188.
38.Hirsch C, Ingelmark BE, Miller M. The anatomical basis for low back pain. Acta Orthop 1963;33:1-17.
39.Hirsch C, Paulson S, Sylven B, Snellman O. Biophysical and physiological investigation on cartilage and other mesenchymal tissues. Characteristics of human nuclei pulposi during aging. Acta Orthop Scand 1953;22:175-183.
40.Hirsch C, Schajowics F. Studies on structural changes in the lumbar annulus fibrosus. Acta Orthop Scand 1953;22:184-231.
41.Inerot S, Heinegard D, Audell L, Olsson SE. Articular cartilage proteoglycans in aging and osteoarthitis. Biochem J 1978;169:143-156.
42.Jessel TM. Neurotransmitters and CNS disease. Lancet 1982;2:1084-1087.
43.Jessel TM, Kelly DD. Pain and analgesia. In: Kandel ER, Schwartz JH, Jessel TM, eds. Principles of Neural Science, Third Edition. Norwalk, CT: Appleton and Lange, 1991:385-398.
44.Johnson EF, Berryman H, Mitchell R, Wood WB. Elastic fibers in the anulus fibrosis of the human lumbar intervertebral disc. A preliminary report. J Anat 1985;143:57-63.
45.Kirkaldy-Willis WH. Managing low back pain. New York: Churchill Livingstone, 1983.
46.Kulak RF, Belytschko TB, Schultz AB, Galante JO. Non-linear behaviour of the human intervertebral disc under axial load. J Biomech 1976;9(6):377-386.
47.Liang M, Komaroff AL. Roentgenograms in primary care patients with acute low back pain. A cost-effectiveness analysis. Arch Intern Med 1982;142:1108-1112.
48.Loeser JD. Perspectives on pain. In: Turner P, ed. Proceedings of First World Congress on Clinical Pharmacology and Therapeutics. London: Macmillan, 1980:316-326.
49.Martin JH, Jessel TM. Modality coding in the somatic sensory system. In: Kandel ER, Schwartz JH, Jessel TM, eds. Principles of Neural Science, Third Edition. Norwalk, CT: Appleton and Lange, 1991: 341-352.
50.Merskey H. Pain terms: A list with definitions and notes on usage. Recommended by the IASP subcommittee on taxonomy. Pain 1979;6:249.
51.Modic MT, Pavlicek W, Weinstein MA, et al. Magnetic resonance imaging of intervertebral disc disease: Clinical and pulse sequence considerations. Radiology 1984;152:103-111.
52.Morgan FP, King T. Primary instability of lumbar vertebrae as a common cause of low back pain. J Bone Joint Surg (Br) 1957;39B:6-22.

53.Naylor A, Shental R. The collagenous changes in the intervertebral disc with age and their effect on elasticity. Br Med J 1954;2:570-573.
54.Osti OL, Vernon-Roberts B, Moore R, Fraser RD. Annular tears and disc degeneration in the lumbar spine. A post-mortem study of 135 discs. J Bone Joint Surg (Br). 1992;74B:678-82.
55.Otsuka M, Yanagisawa M. Does substance P act as a pain transmitter? Trends Pharmacol Sci 1987;8:506-510.
56.Panjabi MM, Krag MH, Chung TQ. Effects of disc injury on mechanical behaviour of the human spine. Spine 1984;9:707-713.
57.Payan DG, McGillis JP, Goetzl EJ. Neuroimmunology. Adv Immunol 1986;39:299-323.
58.Peereboom JWC. Age-dependent changes in the human intervertebral disc. Gerontologia 1970;16:352-367.
59.Rexed B. The cytoarchitectonic organization of the spinal cord in the cat. J Comp Neurol 1952;96:415-495.
60.Rockoff SF, Sweet E, Bluestein J. The relative contribution of trabecular and cortical bone to the strenght of human lumbar vertebrae. Calci Tissue Res 1969;3:163-175.
61.Siddal PJ, Cousins MJ. Spinal pain mechanisms. Spine 1997;22:98-104.
62.Sullivan JD, Farfan HF, Kahn DS. Pathologic changes with intervertebral joint rotational instability in the rabbit. Can J Surg 1971;14:71-79.
63.Twomey L, Taylor J, Furniss B. Age changes in the bone density and structure of the lumbar vertebral column. J Anat 1983;136:15-25.
64.Vanharanta H, Sachs BL, Spivey M, et al. A comparison of CT/discography, pain response and radiographic disc height. Spine 1988;13:321-324.
65.Vernon-Roberts B, Pirie CJ. Degenerative changes in the intervertebral discs of the lumbar spine and their sequelae. Rheum Rehab 1977;16:13-21.
66.Weinstein JN. Anatomy and neurophysiologic mechanisms of spinal pain. In: Frymoyer JW, ed. The Adult Spine: Principles and Practice. New York: Raven Press, 1991:593-610.
67.White AA III. The 1980 Symposium and Beyond. In: Frymoyer JW, Gordon SL, eds. New Perspectives on Low Back Pain. Park Ridge: American Academy of Orthopaedic Surgeons, 1989:3-18.
68.White AA, Panjabi MM. Clinical Biomechanics of the Spine. Philadelphia: Lippincott, 1978.
69.Wurster NB, Lust G. Fibronectin in osteoarthritic canine articular cartilage. Biochem Biophys Res Commun 1982;109:1094-1101.
70.Wurster NB, Lust G. Synthesis of fibronectin in normal and osteoarthritic articular cartilage. Biochem Biophys Acta 1984;800:52-58.