

SPINAL DYSFUNCTION AND PAIN: RECENT ADVANCES IN BASIC SCIENCE

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INTRODUCTION

The following review summarizes some recent advances in our understanding of back pain. It is a selective account, which attempts to show how advances in different scientific disciplines can be combined with each other to form a "natural history" of back pain. A full exposition of these ideas, and of the experimental evidence which supports them, can be found in: "The Biomechanics of Back Pain", published recently by Harcourt Brace¹⁴

ADVANCES IN ANATOMY: WHICH TISSUES ARE PAINFUL?

Obviously, synovial joints, muscles and fascia are innervated and capable of giving rise to pain. Intervertebral discs also can be a direct source of pain, and the unique mechanical properties of these structures may explain some of the unusual characteristics of back pain. Gross anatomical studies have indicated that the outer posterior annulus fibrosus is innervated by branches of the sinuvertebral nerve, a mixed somatic/sympathetic nerve which starts in the intervertebral foramen and forms a dense plexus in the posterior longitudinal ligament^{19,41}. Recent histological studies using immunohistochemical staining techniques have confirmed that nerve fibers penetrate the outer few millimeters of annulus in healthy discs⁵⁷. Further in growth into the center of the disc is presumably inhibited by the hydrostatic pressure conditions that exist in the nucleus and inner annulus of healthy discs⁹: this pressure would act to collapse any hollow blood vessels on which nerves depend. However, degeneration causes the nucleus and inner annulus to lose their

hydrostatic properties⁹, and this may explain why nerves can grow into the center of degenerated and painful discs²³.

Anatomical studies can indicate that a tissue is *capable* of signaling pain. Direct evidence that certain tissues *are* painful must come from pain-provocation and pain-blocking studies on sedated patients. These have shown that the posterior annulus is the most frequent source of severe low back pain, followed by the sacroiliac and apophyseal joints^{42,63,61,62,64}. Muscles and ligaments tend to cause very localized back pain, and nerve roots cause leg pain⁴².

ADVANCES IN EPIDEMIOLOGY: GENETIC INFLUENCES IN SPINAL DEGENERATION AND PAIN

Studies on identical and non-identical twins have shown that approximately 70% of intervertebral disc degeneration, and 50% of back pain, can be attributed (in a statistical sense) to genetic inheritance^{49,60}. The race is now on to find the genes responsible. Already, several genes which influence the quality and strength of spinal tissues have been implicated, including those which code for collagen Type IX and aggrecan^{15,37}. A gene which influences vitamin D metabolism is also involved in disc degeneration⁷⁰. It is conceivable that some genes could exert their influence through biomechanics, perhaps by decreasing the length of the spinous processes and thereby increasing the forces required to extend the spine (**Figure 1**). Other individual risk factors for back pain such as a long, flat, stiff back¹¹ probably represent the combined influences of genes and environment.

This line of research constitutes a major advance in our appreciation of the underlying causes of back pain, because it means that environmental effects such as heavy manual labor cannot be as dominant as was previously thought. However, environmental effects must still be important because genes are inherited from the moment of conception, and yet do not cause tissue degeneration in children. On the contrary, their detrimental effects on spinal tissues are not normally evident until those tissues have been exposed to the (mechanical) environment for 30-50 years^{32,68}. Also, it is evident that environmental influences are generally easier to manipulate than genetic ones, so strategies for the prevention and cure of back pain are likely to concentrate on environmental rather than genetic influences.

Many epidemiological studies of risk factors for back trouble are limited by methodological difficulties. Inconsistent and non-significant associations are often due to small sample sizes, poor follow-up rates, a failure to quantify risk exposures accurately, or poorly defined outcome measures. For example, associations between "heavy" occupations and back pain often become evident only when the risk factor (spinal loading) is quantified rather than assessed subjectively²⁵. Similarly, physical factors such as poor spinal mobility are unlikely to be significantly associated with self-reported "back pain" because some degree of back discomfort is almost universal, and the decision to report trivial discomfort as "back pain" is dominated by psychosocial factors (see below). However, if the outcome measure is "serious" back pain involving medical consultation or time off work, then the influence of psychosocial factors diminishes and that of

mechanical factors rises¹¹. Even more “serious” and objective outcome measures, such as a disc prolapse confirmed at surgery, are very strongly linked to mechanical loading^{39,53}. Significant links between disc degeneration and pain are unlikely to emerge from studies, which consider any change in the MRI appearance of an intervertebral disc to constitute “degeneration”. True disc degeneration involving radial fissures or disc prolapse is strongly associated with back pain, whereas a loss of MRI signal intensity (which indicates dehydration) is not^{20,52}.

Problems in individual epidemiological studies can be compounded in “systematic reviews” which tend to average-out the results of methodologically sound studies without regard for their scientific insight, and which systematically under-represent the impact of the most informed and incisive investigations. The nihilistic influence of systematic reviews is likely to be especially great if the reviewer lacks expertise in the complex relationships between genes, environment, spinal degeneration, and pain.

ADVANCES IN BIOMECHANICS: STRESS CONCENTRATIONS AND TISSUE DAMAGE

Spinal tissues or structures can be said to be “damaged” if they suffer a permanent impairment in their resistance to deformation. Damage occurs when the applied stress (force per unit area) exceeds some critical value, and this is most likely to happen when the force is concentrated in some small region of the tissue or structure. Stress concentrations within innervated spinal tissues may be able to provoke back pain even if they are not severe enough to cause mechanical damage. This would constitute a mechanical basis for a “functional disorder” in which pain is unrelated to any discernable pathology. Most of the scientific evidence relating to stress concentrations concerns the vertebral column in general, and the intervertebral discs in particular. A recent review has summarized the rather limited progress in our understanding of the sacroiliac joints³¹.

The distribution of compressive stress between the intervertebral disc and apophyseal joints depends very much on posture, which determines the angle between adjacent vertebrae. Lordotic postures concentrate approximately 20% of the compressive force on the inferior margins of the apophyseal joints, whereas moderate flexion ensures that all of the compressive force is resisted by the disc^{1,5}. Full flexion stretches the ligaments of the neural arch and causes the compressive force on the disc to be increased by up to 100% as a result of ligament tension⁵. Sustained (“creep”) loading squeezes water from the discs⁵⁰, reduces their height, and increases loading of the neural arch^{1,24}. Pathological disc narrowing can cause the apophyseal joints to resist as much as 70% of the spinal compressive force¹.

Distributions of compressive stress within the disc itself also depend on posture and loading history. Lordotic and fully flexed postures concentrate stress on the posterior and anterior annulus, respectively, and the former can lead to marked posterior bulging of the posterior annulus in cadaveric experiments (**Figure 2**). Moderate flexion, on the other hand, usually distributes the stress evenly across the entire disc¹³. Several hours of creep loading reduces the pressure in the nucleus by approximately 30-40%, and increases peak

compressive stress in the annulus, usually posterior to the nucleus⁸. Damage to the vertebral body endplate (which is the “weak link” of the spine in compression) causes a 10-50% drop in nucleus pressure, and generates high concentrations of compressive stress in the annulus^{12,4}. There is preliminary evidence from cadaveric experiments¹² and an animal model³³ that these changes can cause the annulus to collapse into the nucleus, which is a common feature of disc degeneration^{29,67}.

If the lumbar spine is flexed for a long period of time (for example during a long car journey, or gardening) then creep stretching occurs in the spinal ligaments⁷. The spine can then move into greater flexion⁴⁸ and the stretch reflexes which normally cause the back muscles to protect the spine from hyper flexion become desensitised⁶⁵. The lumbar discs would then be vulnerable to hyper flexion injuries, including prolapse²

ADVANCES IN MATHEMATICAL MODELS: EXPLAINING MECHANISMS OF INJURY

Finite element models of the spine are increasing in complexity and sophistication. However, their predictions depend greatly on the assumed mechanical properties of spinal tissues, and these properties can be chosen at will from a wide range of experimentally-determined values. Not surprisingly, it is easy to ensure that the model's predictions agree with experimental measurements in validation studies. However, this means that the model has little independent predictive power: it predicts what the modeler has designed it to predict.

Nevertheless, finite element models can be useful in assessing the effects of varying individual parameters on the mechanical behavior of the spine. For example, the fact that discs can prolapse when loaded severely in bending and compression has been established by experiment^{2,3,27}, but models have further demonstrated that disc prolapse under these circumstances is more likely to occur if the disc is loaded rapidly, while fully hydrated, and with the addition of axial rotation^{44,73}

ADVANCES IN CELL BIOLOGY: MECHANOBIOLOGY, TISSUE DEGENERATION AND PAIN SENSITISATION

The old idea that mechanical loading is bad for the back is slowly being replaced by an understanding that only *excessive* loading is likely to cause tissue damage and back pain⁶. In fact, moderate cyclic loading causes an adaptive remodeling response, which can lead to strengthening of muscles, bones²⁶, ligaments⁵⁴ and even intervertebral discs⁵⁹. In life, any tendency for spinal tissues to fail as a result of accumulating wear-and-tear (“fatigue”) damage is offset by their ability to adapt biologically to their mechanical environment: in effect, vigorous physical activity sets up a “race” between these two processes, with the outcome being dependent on the *intensity* of loading, and on the age of the person. By this reasoning, fatigue failure would be most likely to occur in middle aged or elderly individuals, whose skeletal tissues have an impaired ability to adapt to mechanical stimuli⁴⁷, when they suddenly adopt a physically-demanding job or recreational activity¹⁰.

This possibility has not yet been confirmed by epidemiological studies, most of which are cross-sectional and so consider working populations in which long-term survivors with adapted backs are over-represented. However, two prospective studies have provided evidence in support of the idea that it is abrupt *increases* in physical activity (rather than the intensity of activity), which is most harmful to the back^{11,40}.

Lumbar intervertebral discs are particularly likely to lose out in the “race” between adaptive remodeling and fatigue failure, because they are the largest avascular structures in the body. Collagen turnover probably takes more than 100 years in articular cartilage⁶⁹, and in intervertebral discs it may take even longer, so disc would be much slower than muscles or bones to strengthen in response to exercise.

Animal experiments have confirmed that mechanical disruption of skeletal tissues such as ligaments and cartilage leads inexorably to cell-mediated degeneration. As far as intervertebral discs are concerned, the time taken for degeneration to occur varies between days or weeks in small animals, to 15 months in sheep^{36,43,56,58}. In the sheep model of disc degeneration, the cells make some attempt to repair the scalpel-induced disc injury, but this is inadequate, and the structural disruption and histological appearance steadily deteriorate⁵¹. In humans, this process might take several years.

The cellular processes involved in disc and articular cartilage degeneration has been studied in tissue culture experiments. Essentially, very high and very low stresses both inhibit the ability of cartilage cells to manufacture the large collagen and proteoglycan molecules which comprise most of the extra-cellular matrix³⁵. In addition, high stresses over 3 MPa increase the production of matrix-degrading enzymes³⁰. Structural disruption of an intervertebral disc impairs its ability to resist external forces evenly, so that regions of very high and very low stress are generated within the tissue,^{12,4} both of which hinder disc cell metabolism.

It has been assumed for many years that degenerative changes weaken skeletal tissues so that structural failure can occur as a result of normal loading. The experimental evidence reviewed above, however, points in the other direction: it suggests that structural failure comes first, and that degeneration marks a cell-mediated response to that failure.

Degenerated tissues are not always painful. Tissues such as articular cartilage and nucleus pulposus cannot be a direct cause of pain because they do not normally contain any nerve endings, but even when nerve endings are present in a tissue, degeneration can be painless. This could be because the structural disruption evident in degenerated tissues impairs their ability to resist external forces, so they become “stress shielded” by adjacent healthy tissue. For example, severe degeneration reduces the compressive stiffness and height of intervertebral discs, so that most of the compressive force on the spine is resisted by the neural arch rather than the disc¹. Another reason for complicated links between degeneration and pain is that some tissues become painful only when their nerve endings are sensitized by biochemical changes. There is evidence that displaced nucleus pulposus can release chemicals (including nitric oxide²¹) that cause morphological and functional changes in spinal nerve roots⁵⁵, and which cause pain-related behavior in laboratory

animals^{34,38}. This apparent “pain-sensitization” effect of displaced nucleus tissue can be modulated by inhibiting the synthesis of nitric oxide within it²¹.

Aging is closely associated with spinal degeneration, but not so closely that the two processes should be equated. Certain biochemical processes advance inexorably with age in various spinal tissues: these processes include increased cross-linking between adjacent collagen molecules, fragmentation of proteoglycan molecules, and water loss. “Oxidative stress” in poorly vascularized tissues can combine with non-enzymic cross-linking of collagen to create advanced glycation end-products (“AGE’s”) which stain the tissue yellow-brown, and make it stiffer and possibly more vulnerable to injury¹⁶.

The term degeneration should be reserved for processes which are superimposed on top of normal aging, or which indicate a marked acceleration of it. Degenerative processes are probably triggered by some “insult” such as injury, or fatigue failure, or smoking (which probably impairs metabolite transport into the discs¹⁷, and other poorly vascularized tissues). We suggest that a defining feature of degeneration should be structural disruption, because this marks an identifiable stage in the degenerative process which is non-reversible in most tissues, and which is not a necessary consequence of aging. Features of spinal degeneration include disc prolapse and narrowing, vertebral endplate defects, vertebral osteophytes, rupture and fat-infiltration in ligaments, and osteoarthritis in the apophyseal joints.

ADVANCES IN APPLIED PSYCHOLOGY: PAIN BEHAVIOUR

Pain behavior in its widest sense includes the decision to report minor discomfort as “back pain”, taking time off work, care seeking, and responses to treatment. Not surprisingly, questionnaires which attempt to quantify various aspects of a patient’s personality^{28,45,71} or perceptions of their workplace¹⁸ can be successful in predicting these and other aspects of pain behavior. Recognition of the important role played by the psyche in back pain behavior has recently been termed a “Back Pain Revolution”⁷². This revolution has turned so far that it is no longer acceptable to ignore psychosocial influences in any scientific evaluation of a new treatment.

However, this does not mean that psychological traits and work-related problems actually *cause* much back pain: they merely influence how people respond to it. A recent prospective study found that a battery of five psychometric questionnaires were able to explain only 1-3% of future 1st-time low back pain⁴⁶, and psychometric scores are more closely related to trivial back pain than to severe symptoms¹¹.

Perhaps the most useful role for psychometric questionnaires is to identify which patients are likely to develop chronic back pain and disability²². Another potential application of this approach is to devise psychosocial interventions (such as distributing a pamphlet which emphasizes positive beliefs and attitudes about back pain), which can effectively reduce work absence due to back pain⁶⁶.

SUMMARY: HOW DOES THE NEW KNOWLEDGE FIT TOGETHER?

The following account attempts to pull together this new scientific evidence to form a typical “natural history” of back pain. These proposals are summarized in **Figure 3**, where the intervertebral disc is taken to represent spinal tissues in general.

Genetic inheritance can predispose spinal tissues to damage, by weakening them biochemically, by interfering with their metabolism, or by causing them to be subjected to increased mechanical loading.

Aging contributes to tissue vulnerability, primarily by making certain tissues stiffer and more prone to damage. Also, “wear and tear” micro damage increases with age.

Postural habits can lead to painful stress concentrations in innervated tissues, even in the absence of tissue damage or other pathological changes.

Excessive or abnormal loading can precipitate tissue damage, either in a sudden injury or following severe repetitive loading which causes fatigue damage to accumulate faster than the adaptive remodeling response can deal with. Damage leads to an uneven distribution of stress in a tissue or structure.

“Degeneration” represents a cell-mediated response to tissue damage, as the cells attempt to adapt to non-reversible changes in their (mechanical) environment.

Degenerated tissues are not always painful: some are poorly innervated; some are stress-shielded by adjacent healthy tissues; and some appear to require biochemical changes (“sensitization”) before they become painful.

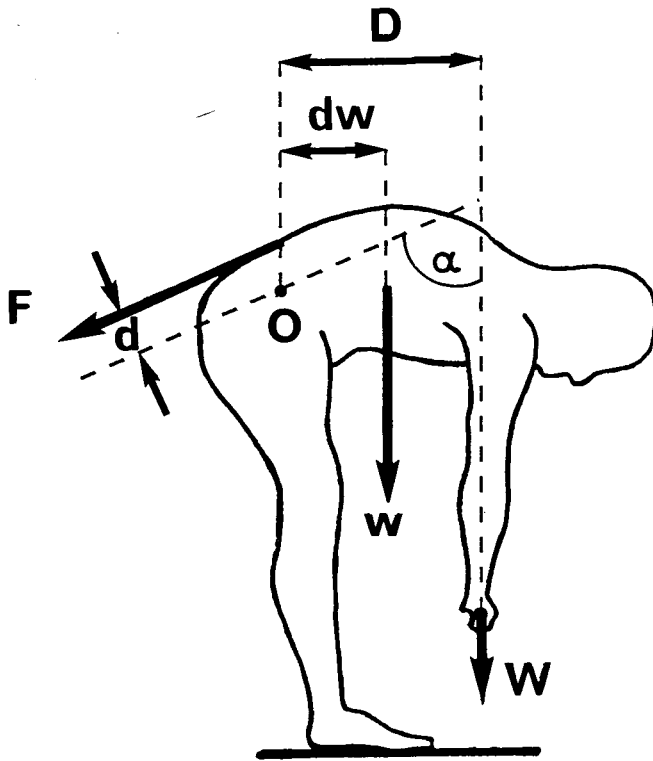
Psychosocial factors influence all aspects of pain *behavior*, including the decision to report back injuries, and respond to treatment.

The current “epidemic” of back pain probably arises from a number of factors, which may include an increased willingness to seek treatment, financial incentives to claim back injuries and disability, and a less active lifestyle which weakens back muscles and spine alike.

In the future, basic science research into low back pain should aim to:

- 1) Identify the genes most closely involved in predisposing particular individuals to spinal degeneration and pain,
- 2) Distinguish between beneficial mechanical loading (which strengthens the spine) and harmful loading (which damages it),
- 3) Explore the cellular mechanisms, which underlie pain sensitization of disrupted tissues, and 4) develop treatment regimes for back pain, which work on the mind as well as the body.

Figure 1. A typical “moment arm analysis” of spinal loading shows how the compressive force acting on the lumbar spine (C) depends greatly on the size of the lever arms D and d. Note that if genetic inheritance caused “d” to be particularly large or small, then this would lead to particularly low or high compressive loading of the spine, respectively.



$$F \times d = W \times D + w \times dw - M$$

$$C = F + (W + w) \times \cos \alpha$$

Figure 2. Photograph of a mid-sagittal section through a cadaveric lumbar intervertebral disc (posterior on right). The hairpin bending of the posterior annulus (arrow) was observed after the specimen was subjected to repetitive mechanical loading in backwards bending and compression. The nucleus (N) appears normal for a disc of this age (M-39, L23).

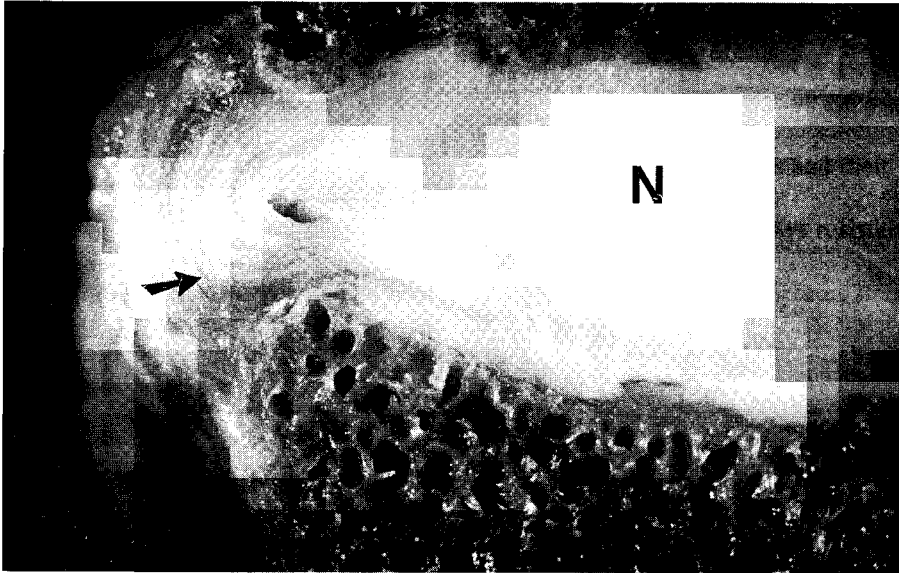
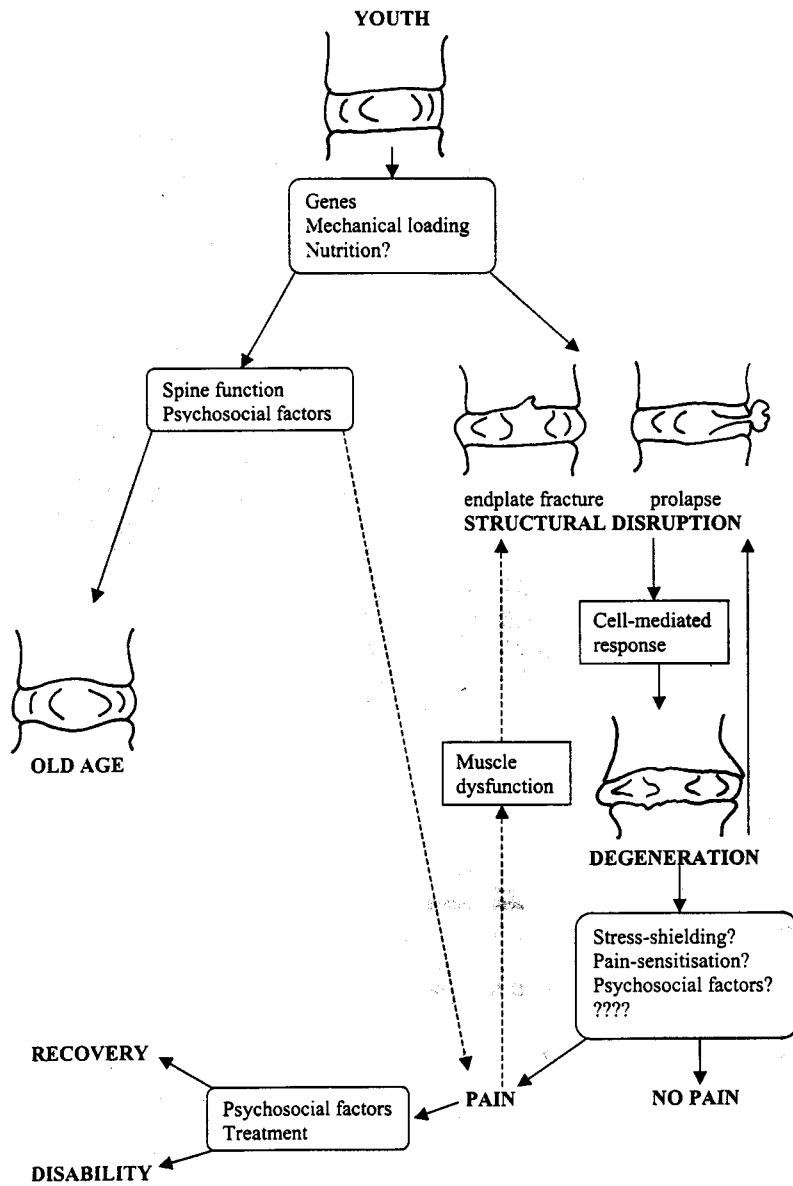


Figure 3. The natural history of back pain, as summarized in the text. Here the intervertebral disc is taken to represent spinal tissues in general. Variable influences are indicated in boxes.



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