Radiculopathy

Learning outcomes;
At the end of this course you should be able to :

1. **Describe the structure of the inter-vertebral disc**
2. **Discuss the biochemical nature of the disc in relation to it's function**
3. **Understand the clinical implications of disc degeneration**

The inter-vertebral disc is a cartilaginous structure sitting between the vertebral bodies which make up the spinal cord. Its main role is thought to be related to shock-absorption and flexibility, but it also shows degenerative change earlier than any other connective tissue in the body. Pathological and degenerative change to the disc structure is clinically significant as it is commonly associated with both chronic back pain and referred pain. This is estimated to cost the UK alone around £12 billion annually, made up of disability benefit, medical care, insurance, and lost working hours. Back pain affects up to 35% of the population, with 10% of patients suffering from chronic disability.

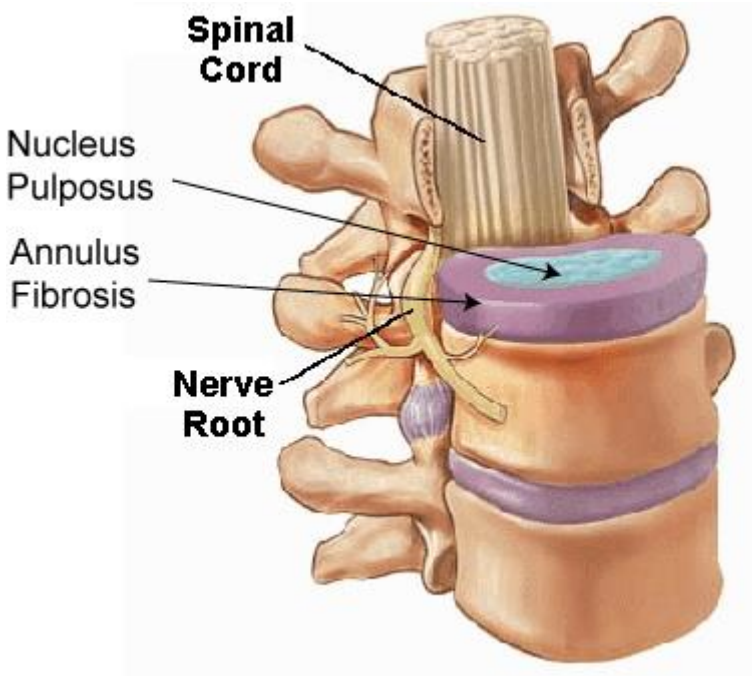
There is a strong association between degeneration of the IV disc with back pain, and whilst many cases of degeneration are asymptomatic, there is a significant association with sciatica, herniation and / or prolapse. Alteration in disc height impacts on the mechanics of the rest of the spinal column, and can adversely affect the relationships between other spinal structures such as muscles and ligaments. In the long term it can lead to spinal stenosis, a major cause of pain and disability in the elderly, and its incidence is rising in-line with the increasing numbers in the elderly population.

It appears that IV discs begin to degenerate earlier than other musculoskeletal tissues. The first clear findings of degeneration in lumbar discs are seen in the age group 11–16 years. Approximately 1 in 5 teenagers

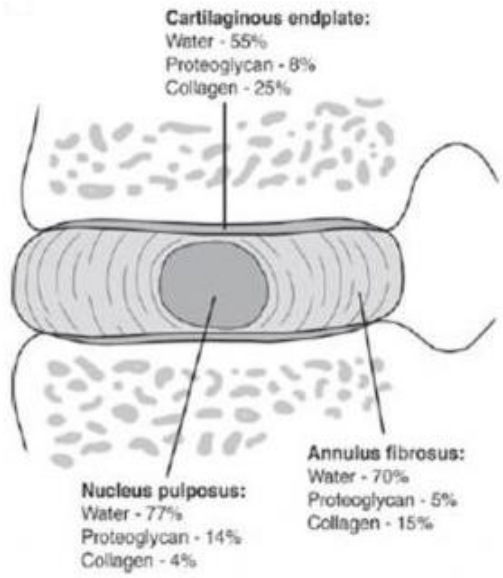
have some signs of mild degeneration, which steadily increases with age, particularly in males, so that around 10% of 50-year-old discs and 60% of 70-year-old discs are severely degenerated.

Disc structure & function

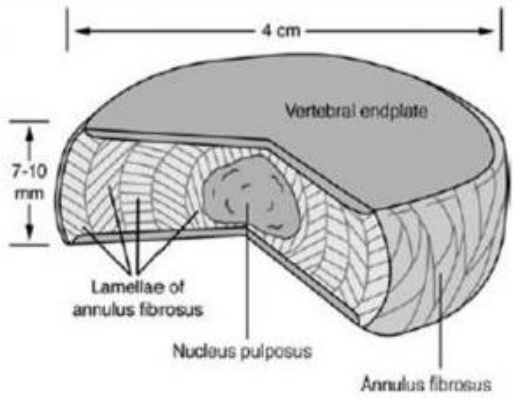
The IV discs lie between the vertebral bodies, linking them together and with which they form symphyses. The discs occupy one-third of the height of the spinal column. Their major role is mechanical, as they constantly transmit loads arising from body weight and muscle activity through the spinal column. They provide flexibility, allowing bending, flexion and torsion. They are approximately 7–10mm thick and 4 cm in diameter (from to back) in the lumbar region. The intervertebral discs are complex structures that consist of a thick outer ring of fibrous cartilage, termed the annulus fibrosus, which surrounds a more gelatinous core known as the nucleus pulposus.



The nucleus pulposus is sandwiched above and below by cartilage end-plates. The central nucleus pulposus consists of a matrix which contains randomly arranged collagen fibres, and radially arranged elastin fibres. Both of these types of protein are embedded within a hydrophilic proteoglycan-containing gel. Interspersed within the gel are chondrocyte-like cells.



Outside the nucleus is the annulus fibrosus, with the boundary between the two regions being very distinct in those under 10 years of age. The annulus is made up of a series of between 15–25 concentric rings, or lamellae, looking similar to the layers of an onion when sliced in half transversely. Each lamellus contains collagen fibres lying parallel to each other within each lamellus at approximately 60° to the vertical axis. The alignment alternates to the left and right in adjacent lamellae, forming a cross-hatched arrangement.



Elastin fibres penetrate through the lamellae, running like holding pins from the periphery to the centre of the disc, binding the lamellae together, possibly helping the disc to return to its original shape following compression, whether it be flexion or extension. The cells of the annulus,

particularly in the outer region, tend to be similar to fibroblasts, being elongated, thin and aligned parallel to the collagen fibres. Toward the inner annulus the cells become more oval.

Cells of the disc, both in the annulus and nucleus, can have several long, thin cytoplasmic projections, and whilst their function is not completely understood, it is possible that they have proprioreceptive abilities, sensing mechanical strain within the tissue. The healthy adult disc has few (if any) blood vessels, but it has some nerves, mainly restricted to the outer lamellae, some of which terminate in proprioceptors.

The cartilage end-plate, a thin layer of hyaline cartilage no more than 1mm thick, lies between the disc and the vertebral body. The end-plate is normally avascular and aneural in the healthy adult. Blood vessels present in the longitudinal ligaments (running vertically up the spinal column) adjacent to the disc, and in young cartilage end-plates under 12 months old, are branches of the spinal artery. Nerves often accompany these vessels, but they can also occur independently, being branches of the sinuvertebral nerve or derived from the ventral rami or grey rami communicantes. Some of the nerves in discs also have glial support cells, or Schwann cells, alongside them.

As the skeleton matures the boundary between annulus and nucleus becomes less clear, and the nucleus pulposus generally becomes firmer and less gel-like. With increasing age and degeneration the disc becomes more disorganised with lamellae becoming irregular, bifurcating and interdigitating. The collagen and elastin networks also appear to become more disorganised, with fissures forming in all areas of the disc. As degeneration progresses, nerves and blood vessels increasingly appear, and cellular proliferation occurs, forming areas of increased density. Apoptosis occurs, and it appears that more than 50% of cells in adult discs are necrotic. In some situations mild cleft and fissure formation have been seen in discs from individuals as young as 2 years of age. As age increases,

degenerative changes progress, but it is not always easy to differentiate between the changes occurring with increasing age and those occurring due to pathological change.

The mechanical functions of the disc are related to the extracellular matrix. The main mechanical role is provided by the two major macromolecular components – collagen and aggrecan. The collagen is mostly types I and II, providing around 70% and 20% of the dry weight of the annulus and nucleus respectively, and providing tensile strength. Aggrecan is the major proteoglycan of the disc and maintains hydration through the osmotic pressure provided by its constituent chondroitin and keratan sulphate chains. The proteoglycan and water content of the nucleus (around 50% and 80% of the wet weight, respectively) is greater than in the annulus (approximately 20% and 70% of the wet weight, respectively). There are also numerous other components, such as collagen types, other proteoglycans (lumican, biglycan, decorin, fibromodulin), and other glycoproteins such as fibronectin and amyloid.

The matrix is constantly being remodelled and replaced. Proteinases such as the matrix metalloproteinases (MMPs) and aggrecanases, are constantly breaking down the structure, but the balance between synthesis, breakdown and accumulation of matrix macromolecules is carefully balanced, and so dictates the mechanical properties of the disc. The integrity of the matrix is also important for maintaining the relatively avascular and aneural nature of the healthy disc.

As age progresses the composition of the matrix changes. The most significant change is the loss of proteoglycan as the aggrecan molecules become degraded. This also results in the loss of glycosaminoglycans, causing a fall in the osmotic pressure of the disc matrix and so therefore a reduction in water content. The collagen population of the disc also changes with degeneration of the matrix, but this is less obvious in comparison to proteoglycans. The overall quantity of collagen may remain fairly constant,

but the types and distribution of collagens will alter. Fibrillar collagens, such as type II, become more denatured due to enzymatic activity, and the triple helix formation is disrupted. In early degeneration it appears that new collagen molecules may be produced, possibly an attempt at repair, but later in the degenerative process this no-longer occurs. Other components may also change, e.g. fibronectin content increases with progressive degeneration, becoming more fragmented. These fragments then feed into the degenerative cascade and it has been demonstrated that they can contribute to the down-regulation of aggrecan synthesis.

Disc degeneration

Changes to oxygen and nutrient supply

Disc degeneration is difficult to study as its definition is somewhat vague, with diffuse parameters that are difficult to quantify. In addition, there is a lack of a good animal model because there are significant differences anatomically between humans and the laboratory animals that are usually used as models of other disorders, most likely due to the differences between bipeds and quadripeds. Particular differences occur in the nucleus pulposus and the cartilage end-plate - in humans the latter acts as a growth plate for the vertebral body whereas in most animals the vertebrae have two growth plates within the vertebral body itself, and the cartilage end-plate is much thinner than the human equivalent. As a result of these differences much of the information on the aetiology of disc degeneration has come from human studies, and therefore is, in some cases, unclear.

A major contributor to disc degeneration is thought to be failure of the nutrient supply to the disc cells. The cells require nutrients such as glucose and oxygen to respire, and it appears that the cells are highly sensitive to changes in extracellular oxygen and pH, with matrix synthesis rates falling steeply at acidic pH and at low oxygen concentrations. The cells do not survive prolonged exposure to low pH or glucose concentrations, so a

reduction in nutrient supply leading to a lowering of oxygen tension or of pH (arising from raised lactic acid concentrations) could therefore affect the ability of disc cells to synthesise and maintain the extracellular matrix, ultimately leading to degeneration.

Discs are avascular and the cells depend on the blood vessels at their margins for metabolic activity. The pathway from the blood supply to the nucleus cells is supplied virtually entirely by capillaries that originate in the vertebral bodies, penetrating the sub-chondral plate of the vertebral body and terminating just above the cartilaginous endplate. Nutrients must then diffuse from the capillaries through the cartilaginous end-plate and the dense extracellular matrix of the nucleus to the cells, a distance of up to 8mm from the capillary bed. Any factor that affects the blood supply to the vertebral body may lead to a significant increase in the rate of disc degeneration. Even if the blood supply remains undisturbed, nutrients may not reach the disc cells if the cartilaginous end-plate calcifies.

Long-term exercise and/ or lack of it appears to have an effect on movement of nutrients into the disc, and thus on their concentration in the tissue. This mechanism is not fully understood, but it may be that exercise affects the architecture of the capillary bed at the disc–bone interface.

Injury and mechanical load

Abnormal mechanical loads are also thought to provide a pathway to disc degeneration. It has always been thought that a major cause of back problems was injury, often work-related, which caused structural damage. It is believed that these injuries initiate a pathway that leads to disc degeneration and finally to clinical symptoms and back pain. Although intense exercise does not appear to affect discs adversely and discs are reported to respond to some long-term loading regimens by increasing their proteoglycan content, experimental overloading or injury to the disc can induce degenerative changes. Further support for the role of abnormal mechanical forces in disc degeneration comes from findings that disc levels

adjacent to a fused segment degenerate rapidly. This is also supported by many epidemiological studies that have found associations between environmental factors and development of disc degeneration and herniation, with heavy physical work, lifting, driving, obesity and smoking found to be the major risk factors for back pain and degeneration. As a result of these studies, there have been many ergonomic interventions in the workplace.

However, the incidence of disc degeneration-related disorders has continued to rise despite these interventions. Over the last two decades, as magnetic resonance imaging has allowed the classification of disc degeneration to be refined it has become evident that, although factors such as occupation, psychosocial factors, benefit payments and environment are linked to disabling back pain, these factors actually have little influence on the pattern of disc degeneration itself.

Genetic factors

More recently it has been suggested that the factors leading to disc degeneration may have important genetic components, with evidence suggesting a strong familial predisposition for disc degeneration and herniation, with heritability being more than 60%. Genetic predisposition has been confirmed by recent findings of associations between disc degeneration and gene polymorphisms (the occurrence of more than one form of a gene) of matrix macromolecules. Although there is a lack of association between disc degeneration and polymorphisms of the major collagens in the disc (types I and II), mutations of lesser collagen types have been strongly associated with lumbar disc degeneration and sciatica.

Other genes associated with disc generation have also been identified, such as polymorphism in the aggrecan gene, leading to aggrecan core proteins of different lengths, with too many of these able to bind only a low number of chondroitin sulfate chains amongst those with severe disc degeneration. These individuals have a lower chondroitin sulfate level than normal, and

their discs will behave similarly to degenerate discs that have lost proteoglycan by other mechanisms.

The findings from these genetic and epidemiological studies suggest strongly that the nature of disc degeneration is multifactorial, and does not merely involve physical and mechanical factors.

Consequences of disc degeneration

The loss of proteoglycan in degenerate discs has a major effect on the disc's load-bearing behaviour - the osmotic pressure of the disc reduces and the disc is less able to maintain hydration under load. Degenerate discs have a lower water content than do normal discs, and when loaded they lose height and fluid more rapidly, and tending to bulge. Loss of proteoglycan and matrix disorganisation have other important mechanical effects, so loading may lead to inappropriate stress concentrations along the endplate or in the annulus.

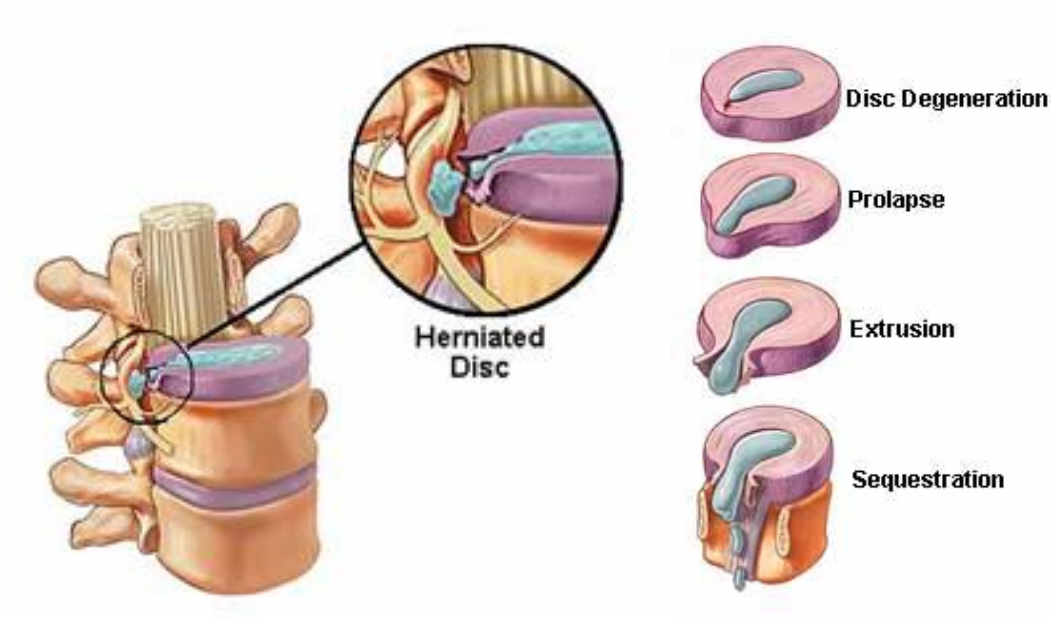
Major changes in disc behaviour have a strong influence on other spinal structures, and may affect their function and predispose them to injury. For instance, as a result of the rapid loss of disc height under load in degenerate discs, apophyseal joints adjacent to such discs (Fig. 1) may be subject to abnormal loads and eventually develop osteoarthritic changes. Loss of disc height can also affect other structures. It reduces the tensional forces on the ligamentum flavum and may cause remodelling and thickening. With consequent loss of elasticity, the ligament will tend to bulge into the spinal canal, leading to spinal stenosis – an increasing problem as the population ages.

Loss of proteoglycans also influences the movement of molecules into and out of the disc. Aggrecan, because of its high concentration and charge in the normal disc, prevents movement of large uncharged molecules such as serum proteins and cytokines into and through the matrix .The fall in concentration of aggrecan in degeneration could therefore facilitate loss of

small, but osmotically active, aggrecan fragments from the disc, possibly accelerating a degenerative cascade. In addition, loss of aggrecan would allow increased penetration of large molecules such as growth factor complexes and cytokines into the disc, affecting cellular behaviour and possibly the progression of degeneration. The increased vascular and neural ingrowth seen in degenerate discs and associated with chronic back pain is also probably associated with proteoglycan loss because disc aggrecan has been shown to inhibit neural ingrowth.

Disc herniation

The most common disc disorder relating to disc pathology is the herniated or prolapsed intervertebral disc. In these cases the discs bulge or rupture (either partially or totally) posteriorly or posterolaterally, and press on the nerve roots in the spinal canal.



Although herniation is often thought to be the result of a mechanically induced rupture it is clear that some degenerative changes are necessary before the disc can herniated. Examination post mortem or of surgical specimens suggest that sequestration or herniation results from the migration of isolated, degenerate fragments of nucleus pulposus through pre-existing tears in the annulus fibrosus. It is clear that herniation-induced

pressure on the nerve root alone is not solely responsible for the cause of pain because more than 70% of 'normal', asymptomatic people have disc prolapses onto the nerve root, without pain. A current hypothesis is that, in symptomatic individuals, the nerves are somehow sensitised to the pressure via the presence of inflammatory mediators and cytokines produced by the damaged cells of the herniated disc. The close physical proximity of the nerve root and disc following herniation may be able to sensitisation of the nerve root. The exact sequence of events and specific molecules that are involved have not been identified, but it is suggested that TNF-α may be predominantly responsible. However, if the inflammatory cascade is interrupted by preventing the release of related cytokines, then molecules such as matrix metalloproteins (MMPs), which are produced extensively in prolapsed discs, will be absent, and it has been shown that these molecules play an important part in the natural history of resorbing the herniation. Many minor herniations heal spontaneously within a few weeks, but severe protrusions may require surgical management.

Clinical presentation

Symptoms will vary depending on the location of the herniation and the types of soft tissue that become involved. They can range from little or no pain if the disc is the only tissue injured, to severe and unrelenting neck or low back pain radiating into the dermatomal region of the spinal nerve/s affected. Often, herniated discs are not diagnosed immediately, as the patients come with undefined pains in the thighs, knees, or feet. Other symptoms may include sensory changes such as numbness, tingling, muscular weakness, paralysis, paraesthesia, and altered reflexes. If the herniated disc is in the lumbar region the patient may also experience sciatica due to irritation of one of the nerve roots of the sciatic nerve. Unlike a pulsating pain or pain that comes and goes, which can be caused by muscle spasm, pain from a herniated disc is usually continuous or at least is continuous in a specific position of the body.

Typically, symptoms are experienced only on one side of the body. If the prolapse is very large and presses on the spinal cord or the cauda equina in

the lumbar region, both sides of the body may be affected, often with serious consequences. Compression of the cauda equina can cause permanent nerve damage or paralysis. The nerve damage can result in loss of bowel and bladder control as well as sexual dysfunction (Cauda equina syndrome).

By far the greatest majority of herniation cases occur in the lumbar region (95% in L4-L5 or L5-S1). This is followed by the cervical region (C5-C6, C6-C7). The thoracic region is least affected, and accounts for only 0.15% to 4.0% of cases.

Herniations usually occur posterolaterally, where the annulus fibrosis is relatively thin and is not reinforced by the posterior or anterior longitudinal ligament.

In the cervical spinal cord, a symptomatic posterolateral herniation between two vertebrae will impinge on the nerve which exits the spinal canal between those two vertebrae on that side.[So for example, a right posterolateral herniation of the disc between vertebrae C5 and C6 will impinge on the right C6 spinal nerve. The rest of the spinal cord, however, is oriented differently, so a symptomatic posterolateral herniation between two vertebrae will actually impinge on the nerve exiting at the *next* intervertebral foramen down.[So for example, a herniation of the disc between the L5 and S1 vertebrae will impinge on the S1 spinal nerve, which exits between the S1 and S2 vertebrae.

Cervical - Cervical disc herniations occur in the neck, most often between the fifth & sixth (C5/6) and the sixth and seventh (C6/7) cervical vertebral bodies. Symptoms can affect the back of the skull, the neck, shoulder girdle, scapula, shoulder, arm, and hand. The nerves of the cervical plexus and brachial plexus can be affected.

Thoracic -Thoracic discs are very stable and herniations in this region are quite rare. Herniation of the uppermost thoracic discs can mimic the clinical presentation of cervical disc herniations, while herniation of the lower thoracic discs can mimic lumbar herniations.

Lumbar - Lumbar disc herniations most often between the fourth and fifth lumbar vertebral bodies or between the fifth and the sacrum. Symptoms can affect the lower back, buttocks, thigh, anal/genital region, and may radiate into the foot and fifth toe. The sciatic nerve is the most commonly affected nerve, causing symptoms of sciatica. The femoral nerve can also be affected, and cause the patient to experience a numb, tingling feeling throughout one or both legs and/or feet, or a burning sensation in the hips and legs.

Management

Current treatments attempt to reduce pain rather than repair the degenerated disc. The treatments used presently are mainly conservative and palliative, and are aimed at returning patients to functional activity. They involve focused rest, analgesia, the use of muscle relaxants, injection of corticosteroids, local anaesthesia, and manipulation therapies.
Disc degeneration-related pain is also treated surgically either by discectomy or by immobilisation of the affected vertebrae, but surgery is not offered frequently in the UK – approximately one in every 2000 back pain episodes, whereas is the USA the incidence of surgical treatment is five times greater. The usual process involves removal of the degenerated disc and fusion of this segment (spinal fusion) with or without metal fixation. Spinal fusion has been one of the main surgical treatments for degenerative

disc disorders with acceptable clinical results, but there are problems associated with spinal fusion surgery, such as accelerated degeneration in the disc adjacent to the fused segment, breakage of fixation, and damage to the nerve tissue during the fixation procedure. In addition, the procedure is highly invasive, costly, and the risk of infection is comparatively high.

Because disc degeneration is thought to lead to degeneration of adjacent tissues and be a risk factor in the development of spinal stenosis in the long term, newer treatments are being developed that are aimed at restoring disc height and mechanical function. To overcome these problems attention has recently turned to biological treatment methods in an effort to stimulate the regeneration process of the degenerated discs. Due to the relatively well encapsulated and avascular environment of the disc, it would seem appropriate to deliver bioactive materials directly into the disc to obtain positive biological effects which can maintain or regenerate disc tissue.

Cell based therapies

The aim of all of these therapies is to achieve cellular repair of the degenerated disc matrix. One approach has been to stimulate the disc cells to produce more matrix. Growth factors can increase rates of matrix synthesis, whereas cytokines lead to matrix loss because they inhibit matrix synthesis whilst stimulating production of agents that are involved in tissue breakdown. Directly introducing growth factors or cytokine inhibitors into the disc has not been successful because their effectiveness in the disc is short-lived.

An alternative approach is gene therapy, which has the potential to maintain high levels of the relevant growth factor or inhibitor in the tissue. In gene therapy, the specific gene is introduced into target cells, which then continue to produce the relevant protein coded for by the gene. However, this therapy is still far from clinical use. Apart from the technical problems of delivery of the genes into human disc cells, the correct choice of

therapeutic genes requires an improved understanding of the pathogenesis of degeneration. In addition, the cell density in normal human discs is low, and many of the cells in degenerate discs are dead, therefore stimulation of the remaining cells may be insufficient to repair the matrix. The implantation of cells either alone or together with gene therapy is an approach that may overcome the low numbers of viable cells.

There is also the possibility of adding new cells to the disc, either on their own or together with an appropriate scaffold. This technique has been used successfully for articular cartilage repair, but currently it's clinical use in humans is limited. The major obstacle is that there is no obvious source of clinically useful cells for the human disc, particularly for the nucleus pulposus. Moreover, conditions in degenerate discs, particularly if the nutritional pathway has been compromised, may not be favourable for survival of implanted cells. However, autologous disc cell transfer has been used clinically in small groups of patients, with promising initial results.

Disc Implantation

One of the newest technologies is artificial disc replacement surgery or disc implantation surgery. Here the biological injured or degenerated disc material is removed and an artificial disc is implanted in the spine. The technology has been used for many years in Europe, but less so in the USA. The development of a stable and lasting prosthetic disc is highly challenging but early designs are promising.

Conclusion

Disorders associated with degeneration of the intervertebral disc impose an economic burden similar to that of coronary heart disease and greater than that of other major health problems such as diabetes, Alzheimer's disease and kidney diseases. New imaging technologies, and advances in cell biology and genetics promise improved understanding of the aetiology, more specific diagnoses, and targeted treatments for these costly and disabling conditions. However, our understanding of the morphology and pathology of

intervertebral discs remains poor, and until this improves it is likely that the situation for patients remains much as it is currently.

KEY LEARNING POINTS.

1. **The IV disc is a cartilaginous structure sitting between the vertebral bodies, providing approximately one third of the height of the vertebral column.**
2. **IV disc problems cost the UK around £12 billion annually.**
3. **The disc comprises a central, jelly-like nucleus pulposus, and a peripheral collagenous annular fibrosis, sandwiched between two hyaline cartilage endplates.**
4. **The annulus is comprised of numerous lamellar rings containing alternately aligned collagen fibres, with elastin fibres penetrating adjacent lamellae.**
5. **There are few blood vessels supplying the disc.**
6. **Disc degeneration is commonest in the lower lumbar discs, and may be related to a reduction in oxygen supply, nutrient supply, mechanical load, and genetic factors.**
7. **Degeneration leads to prolapse / herniation of the disc, which can cause compression on the surrounding structures, specifically the spinal cord and the spinal nerves.**
8. **Compression on the lumbar spinal nerves leads to a loss of motor and /or sensory function in the lower limb, with the classical 'sciatica' presentation.**
9. **Management currently comprises rest and pain relief, and if necessary, surgical decompression of the affected spinal nerves.**
10. **Newer therapies involve gene therapy and disc implantation.**