THE ADHESIVE ARACHNOIDITIS SYNDROME

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INTRODUCTION

"Nam et ipsa scientia potestas est."
(Knowledge is power.)
- Francis Bacon (1561-1626), written in
Meditationes Sacræ. De Hæresibus.

This article aims to give an updated overview of this complex and relatively uncommon condition, with additions to my previous 1999 article of the same title. My aim is to facilitate a clearer understanding of arachnoiditis for both patients and their physicians, so that they can work together to combat the devastating effect the condition can exert upon people's lives.

Many medical practitioners regard arachnoiditis as a rare dinosaur, considering it related to oil-based myelogram dyes, which are no longer in use. This misconception underlies a general tendency to underestimate the ongoing impact of the condition. Far from being a historical curiosity, adhesive arachnoiditis is a 'clear and present danger' which needs to be addressed thoroughly in order to reduce its future impact.

Adhesive Arachnoiditis is a chronic, insidious condition that causes debilitating, intractable pain and a range of other neurological problems. It has been regarded as rare by the medical community, but the true scale of the problem remains unknown for a variety of reasons.

The sad fact is that adhesive arachnoiditis remains a contentious diagnosis, which may reflect the medical profession's reluctance to acknowledge this largely iatrogenic condition. This is not helped by articles such as that by Petty et al ([1]) published in 2000, entitled "Symptomatic lumbar spinal arachnoiditis: fact or fallacy?" in which the authors commented:

"These patients place a heavy diagnostic burden on the treating practitioner", with a concluding comment: "...the diagnosis of '*clinical* arachnoiditis' is essentially a diagnosis of despair or a justification for otherwise unsustainable litigation."

THE SCALE OF THE PROBLEM

Adhesive arachnoiditis is not a notifiable disease and is significantly under-diagnosed. During the Proceedings of the British House of Commons, March 25th, 1998, the issue of arachnoiditis due to Myodil was raised. In answer to the question of the number of cases within the last 20 years, the Under-Secretary of State for Health replied "the information requested is not available" ([2]).

The 2001 New Zealand report by Day et al ([3]) stated:
"It was not possible to calculate the actual population-based incidence or prevalence of arachnoiditis in any form as the clinical data was not available."

Expert Dr. Charles Burton, of the Institute of Low Back and Neck Care, Minnesota, has written extensively about arachnoiditis, and ([4]) has attempted to suggest an estimated figure for cases in the US, using results of an international study that showed lumbo-sacral adhesive arachnoiditis to be responsible for about 11% of all Failed Back Surgery Syndrome cases. Tying this in with the number of surgeries performed in the last 50 years, and an average rate of 25% FBSS, he estimates "at least 1,000,000 FBSS cases in the US would then have been causally and primarily due to the production of lumbo-sacral adhesive arachnoiditis. If one brings in the rest of the world the case estimate would have to be doubled."

Dr. Burton also suggests that between 1940 and 1980 about 450,000 oil-based myelograms were performed in the US every year, giving a total of 19 million*, of which he estimates 5% sustained clinically significant adhesive arachnoiditis (although probably all had anatomical arachnoiditis) as a result, which gives a figure of 950,000 sufferers in the US alone.

Dr. Feffer, in a paper in 1978, suggested that arachnoiditis may occur in about a quarter of the people undergoing an oil-based myelogram and for those having two or more of these procedures, there is as much as a 50% risk of arachnoiditis.

* A promotional leaflet from Lafayette, the US manufacturers of oil-based myelogram dye (iophendylate: Pantopaque), contained the message: "Proven over and over in more than 15 million exams."

Prevalence of arachnoiditis of other aetiology is even less easy to come by. The anaesthetist Dr. J. Antonio Aldrete recently published an article entitled "Neurological deficits and arachnoiditis following neuraxial anesthesia" ([5]) in which he noted "Attempts to identify the frequency with which neurological deficits occur after regional anesthesia have been met with certain scepticism, as a result of the lack of standardized data...and/or recognition of pre-existent neurological diseases." In his conclusion, Aldrete states: "The symptomatology...and the presence of neurologic deficit along with confirmation of arachnoiditis by MRI usually imply that injury to one of the neural structures located intrathecally has taken place. There is need to determine its incidence and all other factors that may render a patient a susceptible candidate for this complication."

Nelson and Landau, in their paper on intraspinal steroids ([6]), remarked:
"it can be estimated that only 0.15%-0.2% of adverse drug reactions will be reported to the FDA. For every reported complication there are probably 400-600 unreported cases! Less than 1% of adverse reports are ever reported in the literature. We must conclude that adverse drug reactions of intraspinal steroid therapy submitted to the FDA (and especially individual case reports in the literature) comprise only the "tip of the tip of the iceberg."

Elsewhere(7), Nelson has estimated that given an assumed maximum of 6% inadvertent spinal taps from epidurals and 20% of patients following intrathecal injections develop clinical arachnoiditis (based on the study by Johnson et al.[8]), the theoretical incidence rate is 1.2%. This figure is considerably higher than data on reported complications suggests.

Burton has called the condition a 'scientific orphan'. In his Burton Report of June 2000([9]), he stated: "There exists no area of medicine today where greater, or more cruel suffering has been produced...than that causally related to adhesive Arachnoiditis... this disease entity remains essentially unknown, unreported and unrecognised."

NOMENCLATURE

It has been suggested in early articles about arachnoiditis that the first mention of the phenomenon of adhesive arachnoiditis was published in 1893 by Quinke, who described a case and outlined the acute and chronic phases of the condition.

In 1897, Schwarz ([10]) wrote about arachnoiditis due to syphilis, listing some symptoms and signs, whilst in 1909, the British surgeon Horsley discussed diagnosis and treatment of "Chronic spinal meningitis."([11])

Later, in1926, in a French medical article entitled ""La Myélite nécrotique subaiguë", Foix and Alajouanine described autopsy cases of spinal arteriovenous malformations which bled into the local areas and caused arachnoiditis. (Blood is a potent irritant to nervous tissue). Progression of the inflammation led to spinal cord damage and paralysis. The syndrome, named after the authors, tended to occur in the thoracic region of the spine.

The term **arachnoiditis** refers to inflammation of the **arachnoid** layer of the meninges - the membranes around the spinal cord and nerve roots. The spinal meninges are in 3 layers, dura, arachnoid and pia. The arachnoid layer of the meninges is part of the **leptomeninges**, the pia being the other.

There have been numerous other terms used, including chronic leptomeningitis, arachnoiditis adhesiva circumscripta, arachnitis, serosa circumscripta spinalis, chemical meningitis, intraspinal granulomatosis and chronic spinal meningitis.

Anatomical or radiological arachnoiditis, (i.e. 'silent', without symptoms) may be relatively commonplace in anyone who has had direct insult (mechanical or chemical) to the arachnoid membrane.

Furthermore, within certain patient populations, notably those with Failed Back Surgery Syndrome (FBSS), adhesive arachnoiditis is more prevalent than many doctors realise; Burton reported as early as 1978([12]) that it is "common in patients with severe back and/or leg pain and functional impairment due to the failed back surgery syndrome."

ANATOMY:

The Meninges: Dura, Arachnoid and Pia.

Dura: The outer membrane surrounding the brain and spinal cord is known as the dura mater, or simply, dura. In the head, the thick grey dura lies right against the skull, with the potential space between the dura and the skull being called the epidural space. After trauma, the arteries in this space can be ruptured and bleed resulting in an epidural haematoma. The space between the dura and the arachnoid membrane is the subdural space. After trauma, some of the veins that bridge this space can be ruptured and bleed, resulting in a collection or pool of blood known as a Subdural haematoma.

The **arachnoid** is a delicate membrane with a fenestrated surface pattern. It is the middle of the 3 meninges that cover the brain and spinal cord. Between the arachnoid and the inner layer (pia) is the **subarachnoid space** in which flows the cerebrospinal fluid (CSF). The CSF is secreted within the ventricles of the brain (fluid-filled spaces deep inside the brain) and the ependymal cells lining the cerebral subarachnoid space. CSF then circulates out and around the brain and spinal cord in the subarachnoid space, being absorbed into the venous sinuses via the arachnoid granulations and via spinal nerve root pockets into the lymphatic system. The fluid provides a protective fluid cushion between the brain and the skull whilst bathing the nervous system with nutrients and removes waste products. Impaired CSF flow therefore prevents this natural exchange from taking place, to the detriment of the affected nerve roots. The entire volume of fluid is produced, absorbed, and replaced about three times per day in a continuous manner. Thus if flow is impeded, this may lead to a build-up of fluid with increasing pressure in the brain (hydrocephalus). CSF flow is seen as a pulse in the dural membrane at operation, but dural pulse is absent in areas where arachnoiditis has obliterated the subarachnoid space, due to impaired CSF flow and hardened dural membrane (pachymeningitis).

Pia: The pia is the thinnest and innermost of the meninges. It is a very delicate membrane, rich in capillaries for blood flow.

ARACHNOIDITIS OR EPIDURAL FIBROSIS?

A frequent question arises about the difference between these two terms. Arachnoiditis is chronic inflammation **inside** the dura, in the arachnoid layer of the meninges (see below) whereas epidural (also called peridural, extradural) fibrosis is scarring **outside** the dural sac. This latter may also be referred to as “adhesions” or “scar tissue”. Many doctors appear to regard epidural fibrosis as less clinically significant than arachnoiditis, but in essence the nerve root compression arising from epidural fibrosis may cause similar clinical problems in terms of lower limb pain, sensory disturbance and weakness. Epidural fibrosis differs from arachnoiditis in that it is more likely to be a localised problem - affecting just one or two nerve roots - and is generally a post-surgical phenomenon, although it may also be a sequela to invasive procedures such as chemonucleolysis.

In cases of arachnoiditis, there is often associated epidural fibrosis, but the reverse is not generally acknowledged, so that patients may be left with a diagnosis of epidural fibrosis and are unable to obtain a diagnosis of arachnoiditis even when the clinical picture fits. Arachnoiditis is an underdiagnosed condition.

PHYSIOLOGY OF SCAR FORMATION

The formation of scar tissue is a normal part of wound healing, in response to injury, whether traumatic or surgically induced. There is a 3-phase repair process: (1) inflammatory, (2) transitional repair and (3) maturation.

Following tissue injury, the initial event involves vascular changes: a brief period of vasoconstriction followed by vasodilatation and at the same time haemocoagulation. This achieves a number of goals: control of bleeding, establishing a mechanical barrier against infection, the apposition of wound margins, and setting up a biological framework within which wound repair may progress.
Another early aspect of wound healing, modulated by inflammatory cells, involves vasodilatation and an increase in blood vessel permeability permitting the influx of agents involved in wound healing. A crucial role is played by histamine, polypeptides and prostaglandins in activation of blood vessel contractile proteins.

Most cells in injured tissue release histamine, which causes brief vasodilatation in adjacent blood vessels. A combination of whole blood exudate and serous transudate creates the typical reddened, hot, swollen, painful area (the cardinal signs of inflammation are dolor: pain, rubor: redness, calor: heat, tumor: swelling). Bradykinins, derived from plasma in the area of the injury, contribute to more prolonged vascular permeability. Prostaglandins, produced by all cells in the body, are released with any breach of cell membrane integrity. Some prostaglandins further contribute to long-term vascular vasodilatation. The fibrin plugs that clotted in the wound also form in the lymphatic vessels.

White cells (leucocytes) enter the inflammatory field: firstly the polymorphonuclear cells (PMN), forming a barrier against infection; and later the macrophages, vital elements in the healing process, responsible for phagocytosis of necrotic tissue, neoangiogenesis (new blood vessel growth) and fibroblast stimulation.

Leucocytes, on arrival at a site of inflammation, release chemical mediators that control subsequent accumulation and activation of other cells. Broadly, these fall into 4 enzyme systems: the complement system, the clotting system, the fibrinolytic (plasmin) system and the kinin system.
Endogenous mediators (produced by the body's immune system) are released at the site of injury by a number of cell types that either contain them as preformed molecules within storage granules, e.g. histamine, or which can rapidly synthesize them as soon as they are required.
Mononuclear phagocytes (monocytes and macrophages) are a central component of inflammation, producing many components which participate in or regulate the different plasma enzyme systems, and hence the mediators of the inflammatory response. They are also actively phagocytic and are involved in microbial killing, as are neutrophils. (The latter are short-lived 'kamikaze' cells, whereas mononuclear phagocytes have a longer life and can also proliferate at the injury site).

Macrophages have 2 important roles in the process of repair. Firstly, they have the job of phagocytosis: by fixing to bacteria, extending their membrane around them, then enzymatically dissolving and digesting them. Optimal phagocytosis requires maintenance of an adequate oxygen supply, so ischaemic tissue, which has impaired oxygen supply, is at greater risk of infection.
Secondly, macrophages act as 'director cells' for repair by virtue of their influence on scar formation. They dispose of necrotic (dead) tissue in the area.
As macrophages ingest microorganisms, they excrete the products of digestion, which include ascorbic acid, hydrogen peroxide and lactic acid, as by-products of phagocytosis. Hydrogen peroxide aids in controlling anaerobic microbial growth, whilst ascorbic acid and lactic acid are thought to signal the extent of damage, their accumulation initiating a further influx of macrophages. Hence there may arise an intense and prolonged inflammatory response; chronically activated macrophages cause a chronic inflammation. Steroids inhibit macrophage levels.
Macrophages may also be involved in vascular regeneration (neovascularisation), which brings oxygen and nutrients into the injured tissue.

Mast cells and basophils, together with platelets, secrete vasoactive mediators. Their function is partially under the control of **cytokines**. The mast cells also release hyaluronic acid and other proteoglycans into the wound area; these bind with the watery wound fluid to create a gel.
Early phase mediators are produced by mast cells and platelets, and include chemoatractants (e.g. C5a) and cytokines such as IL-1, IL-6, and TNF-α.
Later mediators are responsible for the regulation of vascular events occurring from about 6-12 hours after initiation of inflammation. The later vascular events are mediated, at least in part, by products of arachidonic acid.

Other inflammatory mediators may be exogenous (from outside the body) such as endotoxins from bacterial infection, which can trigger complement activation, resulting in the formation of anaphylatoxins which in turn cause vasodilatation and increase vascular permeability.

One of the acute phase reactants is **fibrinogen**, which coagulates in the wound and in the surrounding tissues that are now fluid filled. The coagulated gel later matures into a dense, binding scar. Haematomas, the result of ongoing bleeding in the wound, create more abundant exudate, which may be a stimulus to scar formation. Serous transudate can be diminished by the classic 'RICE' regimen (rest, ice, compression, and elevation). Pharmacological use of steroids and aspirin can target transudative oedema.

The inflammatory phase ends when there is a clean wound bed ready for healing. The macrophages 'direct' the next stage of repair by chemically influencing the number of fibroblastic repair cells activated via a growth factor, which is also produced by platelets. The next phase is **transitional repair**, during which a scar-tissue 'patch' forms. Usually, this stage begins a few days after an injury and lasts a few weeks. However, following severe or repeated injury, or if the scar tissue is damaged, the phase may be prolonged.

This phase has also been termed the fibroplastic phase because it involves fibroblasts as the primary scar tissue producing cells. Migratory fibroblasts follow the fibrin meshwork created earlier in the wound fluid milieu, which bathes all injured structures, thus allowing the fibroblast access to the entire wound. Once in situ, the fibroblast begins synthesis of **collagen**.
Fibroblasts synthesise nitric oxide, which acts as a vasodilator as well as stimulating collagen production by the fibroblasts.

Collagen production involves a highly complex biosynthetic pathway. Each specific collagen type is encoded by a specific gene, the genes for all of the types being located on a various different chromosomes. There are some 20 types of collagen in the body. All have a triple helix structure.
Initially, a precursor form of collagen, called procollagen, is produced. Procollagen contains extension propeptides, which make it very soluble, and therefore easy to move within the cell as it undergoes further modifications. As the collagen molecule is produced, it undergoes many changes, known as post-translational modifications.
One of the first modifications to take place is the very critical step of hydroxylation of selected proline and lysine amino acids in the newly synthesized procollagen protein. Specific enzymes, called hydroxylases, are responsible for these important reactions needed to form hydroxyproline and hydroxylysine. The hydroxylase enzymes require Vitamin C and Iron as co-factors. Hence these are important factors in wound healing. In vitamin C deficient patients, hydroxyproline may be deficient so collagen chains are unable to form in a proper helical structure and thus are weak and easily destroyed.
The trace metal manganese has also been found to be vital for a step called glycosylation, which is important in determining the chemical and structural characteristics of the newly formed collagen and may influence fibril size. Glycosylation enzymes are more prevalent in young people, decreasing with age.
As the procollagen is secreted from the cell, it is acted upon by specialized enzymes, called procollagen proteinases, which remove both of the extension peptides from the ends of the molecule, thus rendering it much less soluble. Parts of these digested end pieces may re-enter the cell and play a part in regulating the amount of collagen synthesis by a feed-back type of mechanism. The processed molecule is now known as collagen and subsequently has a role in fibre formation.

In the extracellular spaces, another post-transitional modification takes place as the triple helical collagen molecules line up and begin to form fibrils and then fibres. This step is called crosslink formation and is promoted by another specialized enzyme called lysyl oxidase. This reaction places stable cross links within (intramolecular cross links) and between the molecules (intermolecular cross links). The crosslink formation is the critical step that gives the collagen fibres strength, which approaches that the tensile strength of steel on a per weight basis. However, scar collagen is weaker than the original collagen, having only a maximum tensile strength of 70-80% that of the original tissue. This is because it does not regain the original structure.

Collagen structure can be visualised by imagining the individual molecules as a piece of sewing thread. Many of these threads, termed fibrils, are wrapped around one another to form a string. These strings then form cords; the cords associate to form a rope and the ropes interact to form cables. The structure is just like the steel rope cables on a suspension bridge.

The final phase, **maturation**, tends to begin 6- 12 weeks after the injury. During this phase, the repair process is a mixture of creation of new normal tissue and breaking down the scar-repair. If there is a disturbance in these processes, an abnormal scar can result.

Collagen Degradation

Of equal importance in the total picture of collagen metabolism is the complex process of collagen degradation. Normally, the collagen in our connective tissues turns over at a very slow and controlled rate of growth. However, after injury, collagen synthesis and remodelling continue at the wound site for some time, in an effort to achieve the original collagen ultra structure. The body is constantly trying to remodel the scar collagen to achieve the original collagen ultra structure that was present before the injury. Collagen degradation requires the activity of a family of enzymes called matrix metalloproteinases or MMPs, which are collagenases. These are synthesised and released by various cells including fibroblasts, macrophages, neutrophils, osteoclasts and tumour cells.
The Rowett Institute in the UK is currently researching the role of collagen metabolism in fibrotic conditions. They suggest, "Fibrotic lesions may be caused by the build-up in the tissue of collagen with the `wrong' type of cross linking. The tissue-specificity of collagen crosslinking appears to be controlled by the enzyme Telopeptide lysyl hydroxylase." ([13])

Fibrinolysis:

Once the tissue repair is complete, fibrinolysis removes the clot or thrombus from the injured tissue. The fibrinolytic pathway is initiated by plasminogen, which is a proenzyme that forms plasmin. Tissue plasminogen activators are found in most tissues, and include *tissue plasminogen activator* (tPA) and *urokinase*. The latter has been used in attempts to break down epidural scar tissue. Plasminogen activator is also a product of macrophages. The level of tissue activator in the plasma is normally low, but can be increased by exercise and stress.

Triggering of fibrinolysis occur when the plasminogen activator, plasminogen, and fibrin are all in close proximity. Both plasminogen and its activator bind strongly to fibrin as the clot forms. This close association prevents inhibition of plasmin activity by inhibitor, and allows proteolysis of the fibrin to proceed after the production of lys-plasminogen. Plasmin inhibitors (*antiplasmins*) that can control plasmin activity include: ?1-antitrypsin, ?2-antiplasmin, C1 inhibitor, antithrombin III.

Plasmin attacks fibrin at a number of different sites, at least 50, reducing its size and forming many fragments, some of which retain the capacity to polymerize, thus competing with fibrinogen for thrombin and acting as inhibitors of clot formation. This may prevent the clot being removed before the tissue is repaired.

Dullerud et al. ([14]) looked at 78 patients who had undergone a previous laminectomy. No evidence of scar formation was seen in 19 patients, a small amount was seen in 36 patients, a moderate amount in 17 patients, and a large amount was observed in 6 patients. More extensive surgery was associated with greater scarring. Fibrinolytic factors tissue plasminogen activator antigen and tissue plasminogen activity were evaluated pre-operatively. It was found that low values were associated with a poor clinical outcome and greater scarring. The authors concluded: "The amount of scar formation after lumbar discectomy seems to be related to the clinical outcome, the size of the surgical exposure, and some fibrinolytic factors."

As we shall see, this concurs with the hypothesis of Jayson, who suggested that a fibrinolytic defect might be responsible for the scarring in arachnoiditis.

Hypertrophic Scarring:

• Overproduction of all components of extracellular matrix

• The normally fine basket weave pattern of collagen in skin is replaced with nodules containing large filaments from fibroblasts

Research:

Growth factors, such as TGF-ß are being investigated with respect to their influence on wound healing.

Beanes et al. recently published an article on the central role of TGF-ß in skin repair and scar formation. ([15]) In the American National Cancer Institute, work is in progress on the role of TGF-ß in wound healing, fibrosis and carcinogenesis. TGF-beta plays an important role in wound healing and is both released from degranulating platelets at the time of tissue injury and produced by fibroblasts and inflammatory cells migrating into a wound site. Numerous studies have shown that systemic or topical TGF-beta can restore normal healing in models of impaired healing. One of the associated 'downstream' proteins, Smad3 is also being investigated, especially in relation to the effect of loss of Smad3 in radiation injury and secondary fibrosis. Smad3 appears to be protective against radiation-induced damage, and selective inhibition of Smad3 activation may be beneficial in wound healing and protective against fibrosis.

The Molecular Neuroscience Research Group at the University of Birmingham (UK), have looked at TGF-ß in deposition of scar tissue in lesioned spinal cord. ([16]) They have also investigated fibroblast growth factor, comparing scarring and non-scarring models of CNS injury ([17]).

Tumour necrosis factor alpha has been found to inhibit Type I collagen synthesis ([18]).

CLASSIFICATION OF ARACHNOIDITIS

Benner classification of arachnoiditis (1978):

0. Extradural compression (spondylosis / stenosis)
1. Local post-operative changes
2. Arachnoiditis at a single level
3. Arachnoiditis at multiple levels
4. Myelographic block secondary to arachnoiditis
5. Arachnoiditis progressive or ascending greater than 2 levels above operative site.

The radiologists classify arachnoiditis according to **Delamarter's MRI classification**:

Type I: central clumping of nerve roots
Type II: peripheral adhesion of nerve roots to the theca ("empty sac")
Type III: complete opacification of the thecal sac, extending over at least one vertebral level

Aldrete describes:
Class I: nerve root sleeves alone
Class II: extends to involve subarachnoid space

TYPES OF ARACHNOIDITIS

The National Organisation for Rare Disorders (NORD) divides the condition thus:

Disorder Subdivisions

- Adhesive Arachnoiditis
- Arachnoiditis Ossificans
- Neoplastic Arachnoiditis
- Optochiasmatic Arachnoiditis
- Postmyelographic Arachnoiditis
- Rhinosinusogenic Cerebral Arachnoiditis
- Spinal Ossifying Arachnoiditis

Under the International Classification of Diseases (ICD-9-CM) the following classification is used for arachnoiditis:

- 320 bacterial meningitis
- 321 meningitis due to other organisms
- 322 meningitis of unspecified cause

Arachnoiditis may be present in anyone who has had spinal injury, surgery or introduction of foreign substances, but in its most common form, **arachnoid adhesions,** tiny areas of scar material, it causes no clinically significant problems in the majority of patients.

The second type is **local arachnoiditis**, which generally results from some local insult to the subarachnoid space, such as injury or surgery. This involves a larger, but still localised area of adhesions which, again, may not cause symptoms. However, this may constitute an undetected 'time bomb' which lurks for years and then precipitates symptoms suddenly apparently out of the blue after a seemingly innocuous event such as a fall or minor car accident. The exact reason for the sudden sustained exacerbation of symptoms and sometimes decline is not known, although it may be due to bleeding into the CSF, with subsequent inflammation and proliferation of scar tissue, to the extent that nerve roots become sufficiently compromised to precipitate overt clinical symptoms and signs.

The most severe type, which is more likely to cause symptoms, is **adhesive arachnoiditis**. This can be mild, moderate or severe, and either focal (localised) or diffuse. The latter type tends to result from insults involving introduction of foreign substances into the subarachnoid space. It may rarely be progressive. In adhesive arachnoiditis arising due to injections into the spinal fluid, (chemically-induced adhesive arachnoiditis), the more widespread damage may also be associated with systemic symptoms.

Spinal adhesive arachnoiditis may be
Localised: at one vertebral level
Segmental: in two or more levels within a spinal region e.g. lumbar
Contiguous: in two or more adjacent vertebral levels
Diffuse: if spread over more than one spinal region e.g. lumbar and thoracic

In the 1999 Global survey, I found the following levels of lesions:

1. Lumbar: 87%
2. Thoracic: 23%
3. Cervical: 34%
4. Cranial: 14% of which brainstem 1 case

Widespread (more than 1 level): 91 cases of which 23 had cranial involvement;
45% of respondents who had undergone an oil-based myelogram had widespread arachnoiditis; compared with 21% of those who had had a water-based myelogram, 27% of those who had unspecified dye, and 8% of those who had had an epidural injection of some kind.

Pachymeningitis

Aldrete ([19]) contends that pachymeningitis is "probably one of the most severe advanced anatomopathological phases" of arachnoiditis, being characterised by proliferation of scar tissue to the extent of encasing the spinal cord and nerve roots. Pachymeningitis affects the dural layer of the meninges.
Wilson ([20]) suggested that the subdural space reacts to the insult of an irritant by producing a well-organised, laminar (layered) fibrosis that resembles a healing subdural haematoma. This level of severity confers serious clinical consequences such as hemiparesis, dysphasia, blurred vision etc.

Arachnoiditis in the cauda equina can cause a **chronic cauda equina syndrome**. This involves pain and sensory disturbance and weakness in the lower limbs, with saddle anaesthesia and bladder, bowel and sexual dysfunction. A rat study ([21]) demonstrated the deleterious effects that cauda equina adhesions have upon supply of nutrients to the nerve roots: in complete cauda equina adhesion, the glucose transport to the cauda equina from the cerebrospinal fluid was reduced by 72% compared with the normal cauda equina. The authors concluded: "Considering the greater nutritional importance of the cerebrospinal fluid in the cauda equina, it is most likely that the impairment of nutritional supply to adhered cauda equina may lead to eventual neural degeneration."

If the spinal cord is affected, there may be areas of ischaemic damage, **myelomalacia** (softening of the tissue) and formation of cysts.

PATHOLOGY

The following stages were described by Burton in 1978:

First stage: **Radiculitis**: the spinal nerve roots are inflamed and the adjacent blood vessels distended (hyperaemia). The subarachnoid space is encroached upon by the swollen nerve roots and practically disappears. Deposition of collagen fibrils (scar tissue) begins.

Second stage: Arachnoiditis: the scar tissue increases, and the nerves become adherent to each other and the dura.

Third stage: Adhesive arachnoiditis: involves complete encapsulation of the nerve roots. The subsequent compression causes them to atrophy. The scarring prevents contact with the spinal fluid in that area. Severe adhesive arachnoiditis may be **obliterative**, causing completely impeded CSF flow within the affected area (and hence loss of dural pulse). There may be cysts containing CSF or oil-based myelogram dye. There may also be calcification or ossification.

Aldrete suggests ([22]) that radiculitis and acute arachnoiditis constitute the inflammatory phase, which can be prolonged and progressive if the individual's immune system over-reacts, or if there are repeated insults. In other individuals, this phase may gradually subside, especially if anti-inflammatory measures are taken. After several months, (4-8) the onset of the proliferative phase may occur, in which the adhesions begin to form.

Long ([23]), a Johns Hopkins neurosurgeon, described the following features of arachnoiditis:
Partial or complete block or narrowing of the subarachnoid space, thickening of the nerve roots, obliteration of nerve root sleeves, irregular distribution of contrast medium with loculation of retained iophendylate, formation of cysts and spinal cord atrophy.

Essentially, the nerve roots resemble over-cooked strands of spaghetti that are entwined and distorted. In the later stages, the nerve roots adhere to each other and pull out to the sides of the spinal canal to adhere to the dura.

In 1983, Hoffman, ([24]) working with dogs, found pre-mortem multilevel blockage of the subarachnoid space, leptomeningeal inflammation, fibrosis, adhesions, cysts and nerve roots embedded in thick bundles of collagen. Hoffman remarked: **"it would seem that the literature on this subject deals with only the most severe clinical examples and that arachnoiditis producing symptoms in the absence of sensory-motor abnormalities is unrecognised."**
He proposed the following grades of arachnoiditis:
Grade 1: inflammatory infiltration of the arachnoid and pia mater, no adhesions.
Grade 2: inflammatory infiltrations, mild adhesions without stenosis of the subarachnoid space, partial minor calcification
Grade 3: inflammation of the leptomeninx with severe adhesions, massive calcification
Grade 4: inflammation of the leptomeninx and nervous tissue, complete obstruction of the subarachnoid space by scar tissue.

Bourne ([25]) suggested that arachnoiditis involves inflammation with proliferation of fibrous tissue that strangles and destroys nerve cells and fibres and engorgement of veins with blood when standing or walking causing increased pressure on the enclosed nerves may explain worsening pain during those activities.

Burton ([26]) noted that adhesions may restrict nerve root mobility, leading to increased incidence of lateral herniated disc symptoms with increased tension, decreased blood flow, or additional trauma.

<u>Effects of Iophendylate</u>

Dujovny et al ([27]) in their dog study used a scanning electron microscope (SEM) to detect the effects of contrast media on the arachnoid membrane. They found that the normal fenestrations of the membrane became closed by a fibrin-like structure after the dye had been used, and there were macrophages present,

indicating inflammation. Iophendylate produced the greatest number of macrophages within the fenestrations.

In some cases, the scar tissue calcifies and may form bony plaques: **Arachnoiditis Ossificans (AO)**, a term introduced by Puusepp in 1931([28]). In most cases, the thoracic cord is affected.

Shiraishi, Crock and Reynolds ([29]) have written about spinal arachnoiditis ossificans. They state that it is a "rare pathological entity" which is precipitated by peridural bleeding and meningeal irritation secondary to surgical intervention. Whilst small plaques of calcified material may be found on the spinal meninges at autopsy in around 75% of specimens, most of these are regarded as benign and are likely to have been asymptomatic. The 1971 proposition by Kaufman and Dunsmore ([30]) reserves the term arachnoiditis ossificans for the clinically significant entity that can cause progressive neurological deficit due to compression of nerve roots and spinal cord.

Slavin et al. ([31]) presented a case of thoracic myelopathy caused by extensive ossification of the arachnoid membrane with an associated intramedullary syrinx. The patient presented with a 9-year history of progressive spastic paraparesis of the lower limbs and bilateral sensory loss to a level of T8. There were no obvious precipitating causes. At operation, on opening the dura, the spinal cord was covered "with a light gray hard shell": calcified arachnoid membrane, "circumferentially encasing the spinal cord like an armor" but not follow exiting nerve roots. There was a smooth outer surface facing the dura and a rough irregular surface facing the spinal cord. One piece was thicker and when removed, left a deep groove on the surface of the spinal cord. A vascular structure resembling a venous malformation was also found. It is unclear whether this malformation was cause (perhaps due to a small haemorrhage resulting in inflammation) or effect (post-compression varicose dilation). Similar lesions have been noted in other cases.

The authors divided cases of arachnoiditis Ossificans into 3 groups:

Type 1: consisting of minute calcifications and ossifications frequently encountered at surgical procedures in asymptomatic individuals. It may be quite extensive causing the arachnoid to appear chalky white. It is frequently associated with adhesive arachnoiditis.

Type 2: a small segment of ossified arachnoid occurs, either an isolated plaque or a thicker piece of metaplastic bone; this may compress the underlying spinal cord or nerve roots. This rarely occurs and has causes such as trauma, haemorrhage and arachnoiditis.

Type 3: the rarest, involves circumferential ossification of the arachnoid around the spinal cord or cauda equina. This almost invariably causes progressive neurological deficit.

The authors proposed 3 different theories of aetiology:

1. Ossification occurs as a result of chronic inflammation: supported by the frequent association with adhesive arachnoiditis. Histological studies have shown formation of bone and signs of chronic

inflammation, whilst CSF inflammatory changes have also been noted. The authors noted the history of infective or chemical insult in some cases, and their known link in causing arachnoiditis. In particular, we should note Carta et al. ([32]) who reported on calcification after Depo-Medrol; Van Paesschen et al. ([33]) reporting on Ossificans and arachnoid cyst after cranial tuberculous meningitis; Tanaka et al. ([34]) AO after repeated myelography and spinal surgery.

2. Formation of bone in the presence of arachnoidal granulations that calcify and ossify over time. Cell clusters were seen in studies early in the Twentieth century. This theory is supported by the presence of arachnoiditis Ossificans in the absence of ongoing inflammation. This includes cases such as that reported by Nagpal et al. ([35]) of ossification with unrelated syrinx. In addition, it is worth noting that meningiomas and arachnoid around them may involve ossification/calcification ([36]). For this reason, the authors suggested that the term Ossificans is misleading and should be **"arachnoid ossification"** to avoid suggesting inflammation is present.

3. The third theory suggests that ossification is analogous to other cases of heterotopic ossification such as that seen in cases of spinal cord injury, ([37]) where ossification involves soft tissue around major joints. The precise cause remains unknown, although a number of associated factors have been suggested: micro trauma, chronic infection, genetic factors, and disturbance of calcium metabolism. Ossification has also been reported in patients with post-traumatic paraparesis or paraplegia without spinal cord injury.

The authors also postulated possible pathogeneses for the association between AO and syrinx formation. These include, as suggested by other authors, focal disturbances of regional blood circulation, which could cause ischaemia in the dura, leading to gliotic changes and eventually intramedullary cavitation. Other possible causes include intramedullary haemorrhage, and other factors for tissue defects. As Errea et al. suggested ([38]), impaired CSF circulation might be the cause, and Slavin et al. found absent CSF flow on cineMR imaging flow studies on their patients. This concurred with the pathogenesis proposed by Milhorat et al. (91)

Kahler et al. ([39]) reported another case of syringomyelia and arachnoiditis Ossificans. MRI revealed the syrinx but not the extensive arachnoiditis, which was noted in insertion of a syringopleural shunt. Post-operative CT clearly showed the extent of the lesion.

Faure et al ([40]) reported a case of AO of the cauda equina, which they suggested was unusual, as AO tends to affect the thoracic and lumbar regions. They suggested that although pathogenesis has been regarded as involving clusters of arachnoidal cells, that in fact the environment induced by arachnoiditis and the consequent disturbance of CSF flow is implicated. The authors reviewed cases of AO in the literature and noted that "mechanical dural sac lesions with probable dural breaching during repeated surgery or following SCI were involved in all but two cases." They proposed that opening the dura could be an important causative factor. They also suggested vascular abnormalities, subarachnoid haemorrhage, spinal cord injury, meningitis, repeated mechanical insult and spinal anaesthesia as predisposing factors.

Ossified arachnoid membrane contains well-formed osteoid tissue, suggesting that the ossification process

is active and progressive. Faure et al. remarked: "The association of ossified arachnoid with contiguous and often extensive dense fibrosis of the arachnoid suggest that ossification is the end point of arachnoiditis." (Citing Whittle et al.[41])

Manabe et al. ([42]) described a patient with venous insufficiency and a fluctuating monoplegia due to compressive Arachnoiditis Ossificans at T11-12. Symptoms appeared monthly lasting a few weeks each time.

Brazilian authors, Mello et al. ([43]) described 3 cases of thoracic arachnoid ossification, associated with sensory and motor symptoms, sphincter dysfunction and inferior limb pain. They noted that calcium deposits tend to occur mainly in the middle and lower thoracic spine "where the majority of trabeculated arachnoid cells are located". The ossification is progressive over time, causing ongoing deterioration in the patient. They suggested that spinal cavitation could be due to spinal cord tethering, stretching, and central cord oedema formation, with cerebrospinal fluid blockage and pulse pressure changes.

They also noted intramedullary cavitation associated with the ossified lesions and suggested that this was due to a lowered CSF pressure distal to the thoracic blockage caused by the lesions, which allowed "development of comparatively higher centrifugally directed intramedullary pressure gradients."

Two cases involved the use of iophendylate dye before the first operation (and one patient had a thoracic meningioma resected) and findings of extensive adhesions at re-operation some years later. However, in the first case, there was no obvious cause for the ossified plaques found at the first operative intervention. In the third case, it appears that meningitis and 4 lumbar punctures were the precipitating factors. The authors therefore remarked that the cyst formation they observed was due to spinal cord deformity resulting from meningioma, arachnoiditis and ossification.

Mello and his colleagues noted that their three cases involved similar presenting features as those reported in the literature, i.e. in women, persistent thoracolumbar and leg pain, crural paraparesis and urinary incontinence.

In private correspondence, Dr. Mello recently told me of a fourth case he had come across, which involved a multiloculated syringomyelia associated with arachnoiditis.

Basilar arachnoiditis

Scarring of the basal meninges with subsequent syrinx formation. This causes predominantly cranial symptoms, including pain at the back of the head. It may result from infection such as tuberculosis, when the CT scan may show hydrocephalus, a basilar arachnoiditis, or intraparenchymal lesions, termed tuberculomas.

Optochiasmatic arachnoiditis: The optic chiasm is the junction between the two optic nerves (from the back of the eyes). Arachnoiditis in this area can arise due to infection (cystercicosis, TB etc.) especially

basal meningitis. Viral infection (poliomyelitis, encephalitis) has also been linked with this type of the condition. Some authors suggest that paranasal sinus infection is a causative factor.
In some cases, there may be a traumatic origin and there have also been cases arising after eye surgery (retained muslin).

Ramina et al. ([44]) described a case of severe optochiasmatic arachnoiditis after rupture of a cerebral aneurysm; the man developed progressive visual loss after a subarachnoid bleed; OA was confirmed during later surgery.

Fujimura et al. ([45]) reported a case of visual disturbance due to optochiasmal arachnoiditis and foreign body granuloma 9 months after surgery for aneurysm in which cotton wrapping was used. The authors recommended the avoidance of use of the cotton sheet close to the optic nerve.

There have been suggestions of three phases of optochiasmatic arachnoiditis:

1) Inflammatory
2) Fibrous
3) Hyperplastic (including proliferation of arachnoidal cells)

Aldrete notes that 4 types of OA have been considered:

1) Parenchymatous
2) Diffuse
3) Adhesive
4) Cystic

Prado and Oribe ([46]) proposed the term *optochiasmatic leptomeningitis*, describing lesions as exudative (oedema plus white cell proliferation), haemorrhagic (haemorrhages with fibroblast proliferation) or productive (a thick membrane with islands of arachnoidal proliferation; hyaline degeneration and calcification)
Balado and Franke ([47]) described deep demyelination in the optic nerve.
The effects of OA may result from direct compression of the arachnoid membrane on the optic chiasm and/or from constriction of the blood supply to the optic nerves.
Clinically, OA manifests initially with fronto-temporal headaches followed by eye problems in one or both eyes: firstly with reduced visual acuity. Both eyes may have loss of visual fields (often central scotoma). Examination may reveal optic disc pallor or papilloedema.
Neuroendocrine manifestations may also occur: gonadotrophin insufficiency (impotence, amenorrhoea) or secondary hypothyroidism may be detected; diabetes insipidus, somnolence, pyrexia may suggest hypothalamic effects in isolated cases.

Diagnosis may be difficult. Visual-evoked potentials may be altered. MR scans may demonstrate localised inflammation in the perichiasmal area. Differential diagnosis includes Multiple Sclerosis (optic neuritis) and Devic's disease.

Cerebral arachnoiditis:

Arachnoiditis affecting the brain is usually related to infections (meningitis), trauma, tumour, intracranial haemorrhage and chemical insult (myelogram dyes). It was reported as early as 1924 by Horrax ([48]) who reported symptoms suggestive of a tumour, but which turned out to be arachnoiditis in the cisterns.
The commonest cause of cerebral arachnoiditis (CA) is infection, whether local (within the CNS) or in other parts of the body, particularly the sinuses and the middle ear. Tuberculous CA has been shown to arise in the absence of pulmonary infection. Cystercicosis is a parasite that can cause this type of arachnoiditis.

A study in the late 1980s looked at 92 patients with hydrocephalus secondary to cysticercotic meningitis. The mortality rate was 50%, with most patients dying within the first 2 years after cerebrospinal fluid (CSF) shunting, with spontaneous remission of the cysticercotic arachnoiditis, as shown by the CSF findings, occurring in only 18%. The authors noted, "In most patients, arachnoiditis and positive immune reactions persisted unchanged even after several years." ([49])

White ([50]) noted: "Subarachnoid cysticercosis is associated with arachnoiditis. The arachnoiditis may result in meningitis, vasculitis with stroke, or hydrocephalus."

In 1978, a paper ([51]) on parasite infections in Thailand noted, "Cysticercus cellulosae, caused by Taenia solium*, commonly results in epilepsy, and sometimes increased intracranial pressure from intraventricular obstruction or from basal arachnoiditis."
The author went on to remark that spinal cord and cauda equina involvement tend to occur much less frequently and to recommend Cysticercus complement fixation tests on the CSF and computerised axial tomography (CAT scan) as helpful in establishing diagnosis.
* Taenia solium is the tapeworm

Mexican doctors ([52]) reported a case of the 32 year old man who presented with a subarachnoid haemorrhage and was found to have a cerebral aneurysm that was surrounded by "an area of severe arachnoiditis around a cysticercus" (cysticercus being a focus of infection with cysticercosis). Subarachnoid infection of this type may thus present in unexpected fashion.

This echoed similar findings by their colleagues ([53]), who discussed findings relating to 65 patients with stroke associated with neurocysticercosis. They described a "high frequency of subarachnoidal cysts" adjacent to the ischaemic area. 80% of patients with focal cysticercosis presented with a vascular event such as stroke, compared with 20% of those with diffuse cysticercosis. In diffuse cysticercosis, 80% had hydrocephalus, 64% multiple cerebral infarcts and 43% mental disorders. The authors concluded: "Based on the

distribution of cysticercal disease and the severity of concomitant chronic arachnoiditis, it is possible to identify a wide spectrum of cerebrovascular involvement caused by neurocysticercosis."

Russian investigators ([54]) have found that immune indices are affected in cases of labile or progressive cerebral arachnoiditis: aggravation of clinical symptoms is accompanied by a decrease of a number of T-lymphocytes, an increase of the levels of immunoglobulins A and G as well as of P-proteins and of a general activity of serum interferons.

Immune compromised individuals may develop cerebral arachnoiditis in association with unusual infectious diseases such as aspergillosis, as recently reported by a European group ([55]):a previously healthy man was found, after some fourteen months of chronic meningitis, ventriculitis, choroid plexitis, and lumbar arachnoiditis, complicated by acute hydrocephalus, to have an Aspergillus organism in the cerebrospinal fluid. Eosinophilic aseptic arachnoiditis has been seen in HIV patients ([56]).

Cerebral arachnoiditis has also been noted in cases of sarcoidosis. Bahr et al. ([57]) noted: "Communicating hydrocephalus with sarcoid arachnoiditis is the most common finding" in sarcoidosis of the central nervous system.

Rhinosinusogenic arachnoiditis:

This subtype of cerebral arachnoiditis has been used mostly by Russian authors describing cerebral arachnoiditis as a complication of sinusitis (rhinosinusitis). In 1986, for example, two Russian authors ([58]) reported on 100 patients with rhinosinusogenic cerebral arachnoiditis, of which "Seventy-eight patients presented optochiasmal arachnoiditis: 12 had trigeminal neuralgia; 1, arachnoiditis of the cerebellopontine angle; 6, arachnoiditis of the convex surface of the brain; and 3, the hypertensive hydrocephalic syndrome due to occlusion of the CSF routes." The authors made specific note of the need to image the sinuses when an intracranial inflammatory condition is suspected, as they may be a source of infection.

In 1994, Gushchin ([59]) reported on 66 patients with rhinosinusogenic cerebral arachnoiditis (RCA). He remarked that it "occurs most frequently in subjects suffering from chronic purulent axillary sinusitis or recurrent polysinusitis" and that intracranial abnormalities tend to be more marked on the side where the sinus infection is worst.

The following year, Gushchin ([60]) described the clinical characteristics of RCA, noting that it tended to be a "diffuse cerebral arachnoiditis with predominant pathology meninges of anterior cranial space (66.9% of patients)". Clinical features included: supraorbital head pain with a feeling of pressure on the eyes and painful eye movements as well as abnormalities of smell sensation.

Complications of arachnoiditis include:

Arachnoid cysts:

A "cystic and adhesive" arachnoiditis was described by Benini and Blanco ([61]), in which the cysts are collections of spinal fluid walled off by the meningeal adhesions. Arachnoid cysts are particularly seen after

Pantopaque myelography, where the dye has become encysted rather than as in other cases, persisting as a diffuse thin film. They may also be associated with epidural anaesthesia. Lee and Cho ([62]) suggest that "Intradural spinal arachnoid cysts appear to result from an alteration of the arachnoid trabeculae; some such cysts are ascribed anecdotally to previous trauma or arachnoiditis, whereas the majority are idiopathic and congenital."

Cysts may be spinal, or intracranial (most common locations are the middle fossa (near the temporal lobe), the suprasellar region (near the third ventricle) and the posterior fossa, which contains the cerebellum, pons, and medulla oblongata.), where they are associated with headache and seizures, with focal neurologic signs occurring less frequently. Pathologically, arachnoid cyst walls are formed from a splitting of the arachnoid membrane, with an inner and outer leaflet surrounding the cyst cavity, the cyst wall consisting of fibrous connective tissue slightly denser than normal arachnoid tissue.

Sato et al ([63]) suggest that spinal intradural cysts are "uncommon and rarely cause neural compression".

They note that the lining of the cyst may or may not be arachnoidal tissue. A number of terms are used in the medical literature so that the term arachnoidal cyst may be regarded as synonymous with: extradural arachnoid cyst, sacral meningocele, arachnoid pouch, arachnoid diverticula and meningeal cyst.

Nabors et al. ([64]) classified spinal meningeal cysts as follows:

Type I: extradural cysts without nerve root fibres IA: extradural meningeal (arachnoid) cyst; IB sacral meningocele

Type II: extradural cyst with nerve root fibres Tarlov perineural cyst; spinal nerve root diverticulum

Type III: intradural cysts: intradural arachnoid cyst

The authors suggested that spinal meningeal cysts account for 1-3% of all spinal tumours and occur most frequently in the thoracic spine (65%), then lumbar/Lumbosacral (13%), thoracolumbar (12%), sacral (6.6%) and cervical spine (3.3%). Most of the lesions occur posteriorly in the spinal canal.

Thoracic cysts occur more in adolescents whereas sacral cysts are found more often in adults.

Josephson et al. ([65]) postulated a hypothesis explaining how spinal cord cysts form secondary to obstructions of the spinal canal such as caused by arachnoiditis. Using rats, they used ligation to achieve thecal sac constriction, which caused oedema either side of the ligation within 3 weeks and later cysts developed after 8 to 13 weeks. The authors found that "induced intramedullary pressure gradients originating from cerebrospinal fluid pulse pressure may underlie cyst formation in the vicinity of spinal canal obstructions and that cysts are preceded by edema."

Shah et al. ([66]) noted, "Acquired arachnoid cyst formation can occur with arachnoiditis of various aetiologies."

Santamarta et al. ([67]) looked at the pathophysiology of arachnoid cysts. Cine-mode MRI showed 2 patterns of CSF flow within the cavity; some were harmonic with a patent flow entry zone; these patients tended to have non-progressive and non-localising symptoms and did not require surgical intervention. Those with a more chaotic pattern of CSF flow with swirls throughout the cardiac cycle had a "more disabling clinical picture". Endoscopy revealed that arachnoid cysts "always and variably" communicate with the subarachnoid space, CSF entering the cyst through a patent entry zone or via minute perforations within the arachnoid network, acting as a flexible mesh to modify the area of flowing CSF. Poorly channelled slipstreams of CSF within the cyst can cause damage to the surrounding tissue.

Kumar et al. ([68]) recently described 2 cases of symptomatic spinal arachnoid cysts. These were of the noncommunicating intradural extramedullary type, which are more rare than communicating intradural extramedullary cysts. They are a very rare cause of spinal cord compression and can rarely present with bizarre symptoms, such as angina. Both cases involved spinal cord compression that was relieved by surgical intervention. They noted that arachnoid cysts are typically located in the midthoracic region dorsal to the spinal cord. As the thoracic spinal canal is relatively small in diameter, cysts here tend to become symptomatic. Usually intradural arachnoid cysts present in adolescence or early adulthood.
The authors divided intradural arachnoid cysts in adults into 5 categories:

1) Congenital
2) Arachnoid adhesions secondary to inflammatory process caused by infective agents (virus/bacteria/spirochaete)
3) Arachnoiditis secondary to subarachnoid haemorrhage, contrast media, spinal anaesthetics, meningitis, fibrin glue and bone dust
4) Trauma, lumbar puncture, intradural spinal surgery
5) Idiopathic (unknown cause)

They also discussed the various postulated theories as to the mechanism for enlargement of the cysts:

1. Secretions of cells within the cyst wall
2. Unidirectional valves
3. Pathological distribution of arachnoid trabeculae leading to a diverticulum.

Agnoli et al. ([69]) have hypothesised that these trabecular cells degenerate which causes an increased osmotic pressure within the cyst and thus transudation of fluid into the cyst. Kumar et al. found arachnoid trabeculation and septation in both their cases.

Jean et al. ([70]) described 3 cases in which cervical arachnoid cysts caused spinal cord compression after repeated surgical decompression for Chiari II malformations. All three children were treated for neural tube defect and later developed anteriorly situated arachnoid cysts compressing the brain stem and/or cervical cord. The authors noted that an association between spinal arachnoid cysts and neural tube defect had previously been reported. However, these were cases of previously undetected cysts which seemed to develop after craniocervical decompression. The authors suggested that the CSF dynamics were altered by the surgery, causing alternating compression and dilation of the anterior subarachnoid space. They also noted that arachnoiditis might cause the CSF to become loculated and act as a mass.

Lee and Cho ([71]) described 3 children with symptomatic intradural arachnoid cysts. One was at T12-L1, compressing the conus medullaris, presenting with neurogenic bladder and cauda equina syndrome; the second was at C5-T1, causing spastic gait and neurogenic bladder; the third was at T2-3, presenting suddenly after playing skipping rope. The authors remark that spinal arachnoid cysts are "relatively

uncommon" and specifically the intradural type are "even less common". They are usually asymptomatic but can cause symptoms that come on suddenly or gradually. The MRI scans of the cases demonstrated the intradural arachnoid cysts with slightly lower CSF signal intensity on the gradient echo images and slightly higher signal intensity on T1-weighted images.
The authors suggested that intradural spinal arachnoid cysts "appear to result from an alteration of the arachnoid trabeculae". They noted that some are associated with a history of trauma or with arachnoiditis. Most are located posterior and in the thoracic region.

Lumbosacral arachnoid cysts can cause cauda equina syndrome. Ziv et al. ([72]) looked at 2 children with cauda equina compression due to spinal arachnoid cysts. One had neurogenic bladder dysfunction causing recurrent urinary tract infection, sensory loss in the lower limbs and abnormal tendon reflexes; the second had an unstable gait due to weakness and reduced sensation in the legs. MRI demonstrated cysts in both cases. The authors concluded that lumbosacral arachnoid cysts are a rare cause of cauda equina syndrome in children.

Perineural Tarlov cysts, especially if multiple, can also be a cause of cauda equina syndrome, as first described by Tarlov himself. Nicpon et al. ([73]) discussed a case of an 80 year-old man presenting with cauda equina features, which were found to be due to a number of Tarlov cysts in the lumbosacral region. Zarski and Leo reported that Tarlov cysts cause 7.3% of pain syndrome cases.
Paulsen et al. ([74]) showed that MRI revealed Tarlov cysts in 4.6% of patients although only 1% were symptomatic as a result. The authors stated: "Lumbosacral perineurial cysts are common lesions that are usually asymptomatic but may cause pressure symptoms". They suggested that whilst cyst puncture can alleviate the pain, the cysts repressurise causing return of the symptoms in most cases.

Voyadzis et al. ([75]) looked at 10 cases of Tarlov cysts. They noted that these cysts are found most often in the nerve roots in the sacral region. 7 of the patients, who were symptomatic, had cysts larger than 1.5cm in diameter, causing radicular pain or bladder/bowel dysfunction. 3 had smaller cysts associated with non-radicular pain. Histopathological examination of specimens from 8 patients demonstrated nerve fibres in 75% of cases, ganglion cells in 25% of cases, and evidence of old haemorrhage in half. The authors suggested: "Tarlov cysts may result from increased hydrostatic pressure and trauma."

Nadler et al., ([76]) reporting on a case of a Tarlov cyst presenting as S1 radiculopathy, noted that the patient had had a normal MRI report, although review showed Tarlov cysts within the sacral canal at level S2 with compression of the adjacent nerve root. This accounted for the patient's presenting symptom of posterior thigh pain.

Shaw et al. ([77]) reported a case of cauda equina syndrome with multiple lumbar arachnoid cysts in a patient with ankylosing spondylitis. The authors noted that early intervention is necessary before irreversible damage is done to the cauda equina.

Shih et al. ([78]) presented a case of a 9 year-old girl who developed paraparesis and cauda equina syndrome as a result of an anteriorly located intradural arachnoid cyst.

Tsumoto et al. ([79]) reported a case of thoracic intradural arachnoid cyst presenting as Brown-Sequard syndrome. Interestingly, myelography and CT myelography failed to show the cyst wall. The authors noted that all 7 previous cases in the literature showing incomplete features of Brown-Sequard syndrome, all were at mid-thoracic level and 4 were in the midline. They suggested that the laterality of the lesion and the asymmetrical circulation in the watershed area were important factors.

Spinal cord damage: an animal study ([80]) showed proliferation of fibrous tissue, lymphocyte infiltration and that the pial blood vessels were obliterated. Within the adjacent spinal cord there were multiple small areas of demyelination. Cavitation of the cord was observed in areas where there was ischaemia (lack of blood supply).

Myelomalacia (thinning of the cord) can result from arachnoiditis.
Jain, Jena and Dhammi ([81]) in India, looked at tuberculous Myelopathy. They noted: "The magnitude of thinning of cord did not always correlate with severity of neural deficit, however, thinning of cord in association with myelomalacia carried a bad prognosis" and suggested, "MRI changes in dura-subarachnoid complex suggesting arachnoiditis generally correlated with poor neural recovery."
Milhorat et al. ([82]) included arachnoiditis as a cause of damage to spinal cord tissue, which may lead on to cavity formation within the cord.
In a study of autopsy cases, Milhorat later looked at spinal cord cavitation in syringomyelia. (See below). Extracanalicular (parenchymal) cavities were particularly associated with myelomalacia.
Torres et al. ([83]) reported 7 cases of spinal arachnoiditis as a complication of peridural anaesthesia. All 7 had arachnoid cysts and 5 had cord cavitation. One case had Chiari malformation, one had tethered cord and a third had spinal cord atrophy. The authors suggested: "Meningeal inflammation may have left scars which later induced ischemia and subsequent cavitation. Alternatively, CSF circulation blockade may have dilated the central spinal canal causing ischemia by compression, followed by myelomalacia and cavitation."
Similarly, Sklar et al. ([84]) looked at 8 patients with intradural abnormalities due to epidural anaesthesia. 2 of these had "Associated intramedullary cysts and myelomalacia"

A **pseudomeningocele** may occur, in which there is a secondary 'false' sac adhered to or behind the dura. Pseudomeningoceles are uncommon complications of lumbar surgery developing as a consequence of incidental dural tears. They are encapsulated cerebrospinal fluid collections, typically located in the paraspinal compartment. Both meningocele and pseudomeningoceles are collections of spinal fluid that communicate with the CSF; however, the CSF in meningocele is surrounded (and confined) by the dura whereas, the CSF of the pseudomeningocele is surrounded by paraspinous soft tissues. Because they have

no confining membrane pseudomeningoceles tend to enlarge as more and more fluid escapes from the subarachnoid space into the soft tissue pseudomeningocele and may occasionally reach the subcutaneous space.

Toohey et al. ([85]) reported on 6 cases of post-operative pseudomeningocele which they attributed to use of Adcon-L, an anti-adhesion agent. In 2 cases an intra-operative dural tear was recognised and treated at the time.

Syringomyelia (cavity) is another complication of arachnoiditis, probably arising from the pressure dissociation between the subarachnoid space and the central canal.

In the 1999 Global survey, there were 6 cases of syringomyelia.

Inoue et al. ([86]) looked at 7 patients with syringomyelia associated with adhesive spinal arachnoiditis. They found thoracic cavities in 5, cervicothoracic in 1 and an extended cavity from C4 to L1 in the remaining patient. All cases showed cord deformity due to adhesion or displacement due to an associated arachnoid cyst.

Klekamp et al. ([87]) described foramen magnum arachnoiditis without Chiari malformation as a "rare cause of syringomyelia". They reported 21 cases, and noted accompanying hydrocephalus in one case, and arachnoid cyst in a further case.

In 1990, Caplan et al ([88]) proposed that arachnoiditis causes syrinx formation by obliterating spinal blood vessels, thereby causing ischaemia. Small cystic areas of myelomalacia may form, and these tend to coalesce to form cavities.

Alteration of spinal fluid dynamics due to scar tissue creating spinal block contributes to this process. This was borne out by an animal study in 1992([89]), which concluded from the data that "cavitation within the cord would be induced by the ischemia, and hydromyelia would be produced by the pressure dislocation between the spinal subarachnoid space and the central canal."

Williams ([90]) suggested that post-traumatic syringomyelia might be initiated by the cord being pulled open or by "the development of meningeal fibrosis and adhesion of the walls of the cord to the dura". The subsequent spread of the cavity he ascribed to fluid dynamics within the cavity. He had previously described these effects ([91]), which he termed 'suck' which was the mechanism by which the cavity filled with fluid. This was due to relatively long-standing pressure differences in different parts of the CSF due to arachnoiditis impeding the flow thus allowing pressure dissociation which sucks fluid into the cord in the low pressure area, and to rapid movement within these regions during coughing or sneezing, when the dura is abruptly compressed by distension of the epidural veins, and thus the subarachnoid space is also compressed, so that the fluid is impelled to sudden movement. Williams called these 'rapid impulsive intra-cord fluid movements' "slosh".

He further remarked that in addition to the fluid movements, other pathological processes might be at work in situations such as arachnoiditis secondary to infection or to intrathecal streptomycin, when the

commonest site was in the lower spine. Cavities develop at the point where the cord is at its widest, (much like a balloon will inflate most readily at a point already partially inflated) so that any enlargement is likely to be a focus.

Milhorat et al. ([92]) suggested 3 main types of syringomyelia:

1. Dilatation of the central canal communicating directly with the fourth ventricle
2. Non-communicating dilatation of the central canal below a normal segment of spinal cord
3. Extracanalicular syrinx originating within the spinal cord parenchyma without communicating cavities

The third type tends to be found in 'watershed' areas of the cord and is often associated with myelomalacia; they may be produced by stenosis of the central canal.

Recently, a proposed study on syringomyelia sponsored by the National Institute of Neurological Disorders and Stroke (NINDS), has hypothesised that spinal syringomyelia results from obstruction of CSF flow in the subarachnoid space, which affects spinal CSF dynamics because the spinal subarachnoid space accepts the fluid displaced from the intracranial space as the brain expands during cardiac systole. The reduced CSF compliance and capacity of the theca to dampen CSF pressure waves causes exaggerated waves to be produced with every heartbeat, acting on the spinal cord above the CSF block to drive fluid into the cord. They also suggest a pre-syringomyelic stage when there is spinal cord oedema and progressive myelopathy. ([93])

Australian authors Brodbelt et al. ([94]) recently published the results of their rat study looking at the source and route of fluid flow in post-traumatic syringomyelia, which involved kaolin-induced arachnoiditis. They reported, "Fluid from perivascular spaces moves preferentially into extracanalicular syringes and the surrounding parenchyma. Obstruction to CSF flow and loss of compliance from traumatic arachnoiditis might potentiate fluid flow in the perivascular space."

Non-traumatic syringomyelia

Parker et al. ([95]) conducted a retrospective study of 32 patients treated for syringomyelia associated with non-traumatic arachnoid scarring.18 had extensive scarring, of which 15 were post-meningitis (9 tuberculous, 3 listeria, 3 pyogenic) and 3 were post-subarachnoid haemorrhage. There were 10 cases of focal arachnoid scarring, associated with spinal surgery in 5 (2 meningiomas, 2 neurinomas,1 thoracic disentomb), epidural anaesthesia in 1, thoracic disc herniation in 1, Pott's disease in 1 and 2 of unknown cause. A third group had basal arachnoid scarring without hindbrain herniation, being associated with birth injuries in 4 cases.

Post-traumatic syringomyelia

Brodbelt and Stoodley ([96]) in their recent review of post-traumatic syringomyelia noted that more than a

quarter of spinal cord injury patients develop syringes. They remarked: "The mechanism of initial cyst formation and progressive enlargement are unknown, although arachnoiditis and persisting cord compression with disturbance of cerebrospinal fluid flow appear to be important aetiological factors."

Vannemreddy et al. in Ontario, Canada, ([97]) looked at predisposing factors. They remarked: "PTS follows complete spinal cord injury (SCI) more often than incomplete and is frequently associated with arachnoiditis." Onset of symptomatic PTS tends to be earlier with increasing age, and at cervical and thoracic levels compared with lumbar. Displaced fractures and spinal instrumentation without decompression are also factors.

Post-surgical:

Polish authors Och, Smolka and Kopec ([98]) looked at a case in which removal of a meningioma of the fourth ventricle (cerebral) was followed by development of syrinx at T11-12 eighteen months later, associated with arachnoiditis.

Syrinx in MS

Argentinean authors Gatto et al. ([99]) suggested that "Spinal cord cavitation is a frequent finding in optic neuromyelitis (Devic's syndrome)" whilst being a rare occurrence in patients with the similar condition multiple sclerosis. They looked at 6 patients with DS and 3 with MS. Those with DS all had the relapsing form of the disease but a normal brain MRI. Spinal MRI showed "unenhanced central cavities which extended more than 3 vertebral bodies". In the MS patients, who had the relapsing, remitting form of the condition, had hyper intense T2 enhancing lesions on spinal MRI and non-communicating cavities extending less than 2 vertebral levels.

As we have seen, some people with arachnoiditis have had suspected or proven MS.

A further, uncommon, complication is **communicating hydrocephalus**. This is thought to be due to alterations in the cerebrospinal fluid dynamics, due to the effects of the scarring in the subarachnoid space.

Jensen et al. ([100]) published a paper in the journal Neuroradiology of a fatal case of obstructive hydrocephalus after oil-based myelography; the authors described features typical of the Pantopaque reaction seen in animals. They described postmortem findings of occlusion of the foramina of Magendi and Luschka by granulation tissue and inflammatory features typical of Pantopaque reaction.

Hydrocephalus:

Hydrocephalus secondary to subarachnoid haemorrhage was recently studied by Texan authors Dorai et al. ([101]) They looked at 718 patients with aneurysmal subarachnoid haemorrhage, of which 152 required shunting for hydrocephalus. They found the following associated factors: (i) increasing age, (ii) female gender, (iii) poor admission Hunt and Hess grade (used in assessment during the acute presentation of the haemorrhage) (iv) thick subarachnoid haemorrhage; (v) ruptured aneurysm in distal posterior circulation

(vi) clinical vasospasm, (vii) radiological hydrocephalus at time of admission, (viii) intraventricular haemorrhage, (ix) endovascular treatment.

THE INFLAMMATORY NATURE OF ADHESIVE ARACHNOIDITIS

Arachnoiditis is chronic inflammation of the arachnoid layer of the meninges, which consists of trabeculae, a mesh of interwoven collagen fibrils resembling tissue paper. These are in contact with the spinal fluid, (CSF), which circulates through the cerebrospinal axis.

The initial phase of the inflammatory process involves influx of white blood cells in response to an insult to the subarachnoid space, e.g. an agent such as blood (trauma, surgery), a foreign substance (dye, etc) or an infectious agent (e.g. meningitis). This is initiated via the action of cytokines, (proteins that act as immune modulators). There is infiltration by macrophages and mesenchymal cells; the latter transform into fibroblasts, which make collagen (scar tissue).

Usually the fibrinolytic process, which breaks down excess scar tissue, limits this, but in arachnoiditis the scar tissue persists. Authors such as Jayson ([102]) have suggested that there may be a defect in the fibrinolytic pathway.

A variability in immune response to either the agent causing the injury to the arachnoid membrane or to the injury itself could help to explain why apparently only a minority of patients with arachnoiditis develop the condition to a clinically significant degree.

Agents that trigger inflammation within the arachnoid membrane include exogenous substances such as myelogram dyes, steroid preparations etc. and also, importantly, blood, which is highly irritant. Blood in the subarachnoid space, from a variety of causes including subarachnoid haemorrhage, can alone precipitate reaction that leads to arachnoiditis. Indeed, expert Dr. Antonio Aldrete in his book, "Arachnoiditis: The Silent Epidemic" ([103]) devotes an entire chapter to this problem.

IMMUNE MEDIATORS

- Interleukins
- Tumour necrosis factor; cytokines
- Prostaglandins
- Nitric oxide

Recent studies ([104]) have shown the involvement of matrix metalloproteinases in neuroinflammation in conditions such as multiple sclerosis, meningitis, brain tumours etc. Matrix metalloproteinases (MMPs) are

a gene family of proteases important in normal development, wound healing, as well as a number of pathological processes, such as the spread of metastatic cancer cells, arthritic destruction of joints, atherosclerosis, and neuroinflammation. They have complex roles including release of growth factors, and are important in cell survival and death.

AUTOIMMUNE ASPECTS:

The neurosurgeon Mayfield, through his research in the 1980s, felt that there might be an immune response that is responsible for the degree of reaction, especially to chemical insult. Frank et al cultured arachnoidal cells in vitro and demonstrated their immune capabilities. ([105])
Russian authors ([106]) have discussed changes in the immune indices in cerebral arachnoiditis (rhinosinusogenic and optochiasmatic). Khil'ko et al ([107]) describe a deficiency in immunoglobulin A which they explain as due to " an increase in their consumption due to antigenic aggression in relation to the meninges, which results in extremely low circulating levels of circulating immunoglobulins A." Also Filev et al ([108]) have found persistent viruses in immunocompetent blood cells in cerebral arachnoiditis. However, these findings refer to infective arachnoiditis and it is difficult to know how far they could be extrapolated to spinal arachnoiditis of other aetiologies.

PHYSICAL, CHEMICAL AND EMOTIONAL STRESSORS

Clinical ecology, whilst not a recognised medical specialty, has some interesting observations about the effects of toxic substances on the human body. Clinical ecologists such as Dr. William Rea, founder of the Environmental Health Center in Texas, have followedthe ideas that originated in the 1940s with Dr. Theron Randolph, who asserted that allergies to foods and common substances could cause non-specific symptoms such as fatigue and confusion. They hypothesise that repeated small exposures (or a single high exposure) to environmental agents can sensitise individuals and cause a malfunction in the immune system. Rea defines chemical sensitivity as "an adverse reaction to ambient doses of toxic chemicals in our air, food and water at levels which are generally accepted as subtoxic."([109]) He contends that the reaction will depend on the organ affected, the nature of the toxin, individual susceptibility (genetic, general state of health etc.), length of time of exposure, other stressors and the derangement of metabolism resulting from the original insult.

Looking at Rea's theories about Multiple Chemical Sensitivity ([110]), chemically induced arachnoiditis seems to fit well into his proposed scenario. For instance, in people who have undergone one or more oil-based myelograms, (a high initial insult), there seems to be a higher than normal incidence of the development of multiple allergies (and indeed to autoimmune conditions).

Multiple Chemical Sensitivity (MCS) manifests itself in a broad manner, with non-specific symptoms such as: skin: sores, rashes etc.; eyes: redness, burning, blurred vision; ears: dizziness, balance problems,

tinnitus; nose: congested, nosebleeds; throat: dry, hoarse voice; chest: pain, shortness of breath etc.; gastrointestinal: nausea, vomiting, cramps, diarrhoea; menstrual: irregular periods; musculoskeletal: muscle and joint pain; nervous system: fatigue, headaches, memory lapses, depression, etc.

Rainville et al. ([111]) suggested, "The study of pain may be relevant to the study of chemical intolerance (CI) in many ways". They noted that pain is often reported as a symptom of CI, and that CNS plastic changes in persistent pain states "may share some similarities" with those seen in sensitisation to environmental chemicals. They pointed out that functional brain studies have shown that acute pain is accompanied by activation of a wide network of cerebral regions including the thalamus, which has been shown to be involved in neuropathic pain.

Rea has described phenomena ([112]) such as total body load (total toxic load) which is the amount the body can tolerate (the immune system is like a barrel filled with water, once it is full, it starts to overflow); adaptation (the body adjusts to acute toxic exposure, which depletes its resources, at which point the system can no longer cope, adaptation may mask sensitivity); bipolarity (exposure to pollutants may not cause immediate reaction, but effects may be demonstrated by 'withdrawal symptoms' after the exposure ends); spreading: sensitisation to one chemical leads to reaction to other chemicals; switch phenomenon: transient symptoms migrate from system to system, e.g. joint pain followed by diarrhoea, followed by palpitations.
Assumedly, chemical injection into the spinal area causes the Total body load to be exceeded. As this is directly into the epicentre of the body's neuroimmunomodulatory system, the effect may be more dramatic than in chronic insidious environmental exposure and therefore arachnoiditis might serve as a very useful scientific model for the effects of toxins on the body.

Whilst MCS has yet to be accepted in mainstream medicine, the effects of toxins on the body (e.g. the Camelford incident, silicone implants) are now being recognised and to some extent the explanations offered by doctors such as Rea may help to explain why arachnoiditis sufferers tend to reach a plateau but may then experience a minor trauma which triggers rapid deterioration: one possible explanation is deadaptation: the 'barrel' is full and overflowing and the system is unable to continue to compensate. (In effect, this may be akin to the straw that breaks the camel's back, so to speak).

Chemically induced arachnoiditis (CIA) seems to involve a chronically-hypersensitised CNS, with substantial autonomic effects and centrally-originating pain. This chronic "red-alert" situation then seems to trigger autoimmune problems, presumably via neuroimmunomodulation.

Cruse et al([113]) discuss dysregulation of the sympathetic nervous system seen in spinal cord injury patients(which is similar to that seen in diffuse arachnoiditis) and the consequent effects on the immune system. The sympathetic nervous system is linked with the immune system ([114]), via the hypothalamic-

pituitary-adrenal axis, with cytokines being seen as the immune mediators involved. Sciatic denervation in mice ([115]) has been shown to cause an increase in cell-mediated immunity.

Perhaps another explanation can be advanced: General Adaptation Syndrome
Hans Selye looked beyond the body's immediate response to stress and observed that: (a) Long term exposure to stressful situations can deplete the organism's ability to maintain the stress response, and (b) The pattern of these deleterious effects is independent of the source of stress. In 1956, he outlined a three-stage progression of responses to stress termed the General Adaptation Syndrome: Alarm, Resistance and Exhaustion.
Stage of Alarm. When a stressor is first encountered, the initial series of responses depends upon the autonomic nervous system, the immune system and other defences to cope with the emotional, behavioural and physiological aspects of the stressor.
Stage of Resistance. Involves maintenance of this reaction to the stressor, which includes reparative processes such as fever regulation, tissue repair, control of inflammation, etc.
Stage of Exhaustion. The defences fail, metabolic reserves are depleted, physiological functions undergo a general decline, and serious illness (or even death) ensues.

Note that this general response is independent of the initial trigger event, being more closely related to the interpretation of the environment than to the physical intensity of the aversive stimuli.

In animal experiments, exposure to shock (even if unpredictable and uncontrollable) will not cause physical illness such as stomach ulcers unless the frequency of occurrence is fairly high: an occasional brief shock does not cause this problem.

However, acute trauma such as surgery can lead to the 'shock syndrome' a diffuse outpouring of the entire autonomic nervous system. I suspect this is even more likely if post-operative pain control is sub optimal. In animals, a lack of coping response for acute, profound stressors can cause sudden death through hyperactivity of the parasympathetic nervous system (part of the ANS).

Relatively mild stressors, if not controllable by the individual, can lead to suppression of the immune system, which in turn can increase the vulnerability to diseases, trigger allergies, or lead to autoimmune disorders.

PAIN TRANSMISSION

The International Association for the Study of Pain (IASP) definition of pain is:

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."

A pain system involves receptors that pick up the message, neural pathways that transmit it and analytical centres in the brain to process the information.
Pain receptors are generally referred to as "nociceptors".

Reception:

Somatic nociceptors tend to be polymodal, i.e. they can detect damage due to a variety of stimuli including heat, mechanical trauma, chemical irritation etc. These give rise to burning pain or itch via C fibres and sharp pain via A delta nerve fibres.
Visceral nociceptors are somewhat different. These occur in viscera such as the bladder and gut. They can encode both innocuous and noxious distension of the viscera (innocuous referring to normal distension, noxious to damaging levels of distension). Some only start firing at noxious levels. This may account for what are known as "visceral hyperalgesia syndromes" such as Irritable Bowel Syndrome and Interstitial Cystitis. (Hyperalgesia= increased response to painful stimuli) There may also be referred pain from the viscera e.g. post-sterilisation shoulder pain referred from under the diaphragm to the shoulder tip, or bladder distension may cause pain in the skin of the foot.

In 1996, Dmitrieva and McMahon ([116]) found that "inflammation sensitises visceral primary afferent neurones."-in other words, an episode of inflammation, such as a bladder infection, might sensitise the bladder nerves and trigger an increased response to even normal levels of distension, which may persist well after the infection has resolved.

Habler et al ([117]) found that previously "silent" nerves became active during inflammation. 70% of primary afferents (main sensory nerves) in the bladder cannot be stimulated in the normal physiological situation, but if the bladder is inflamed (e.g. with turpentine in an experimental situation), these neurones start firing.

Investigators have discovered that hypersensitivity to temperature or touch peaks when the numbers of certain immune cells within damaged nerves are highest. This suggests that **cytokines**, small peptides produced by these cells, are involved in mediating pain. A similar process also occurs in the spinal cord, regardless of the original site of injury.

Current research is focusing on identifying the cells that produce various cytokines within the CNS: neurons, microglia and astrocytes (star-shaped cells). Astrocytes produce proteins that change cell function, and appear to play a key role in pain.

Transmission:

Nerve information from nociceptors reaches the spinal cord dorsal horns; this afferent input terminates in various laminae (layers), depending on the type of nerve fibre involved. A large number of secondary order intermediate neurons are then activated. Dorsal horn cells are nociceptor-specific, responding only to noxious stimuli, or multireceptive ('wide dynamic range', 'convergent'), which may also be activated by innocuous stimuli.

Intermediate neurons transmit the information to neurons that connect to the brain (ascending pathways). Numerous different neurotransmitters, some excitatory, some inhibitory, are involved.

Note that input into a spinal nerve root (from a specific dermatome) distributes several segments distally after the afferent has entered the dorsal root entry zone. For example an L5 root may have collaterals extending as far as L1-2.

In the spinal nerve ligation model (nerve is tied tightly) loss of input into the spinal cord might cause upregulation of the excitatory systems (i.e. the system tries to compensate for the reduced or lost signal by becoming more sensitive). This results in hyperexcitability, expanded receptive fields and neurochemical changes in the nerve. This is an example of plasticity, the ability of the nervous system to change.

The spinal nerve ligation model results in a variety of effects, which together tend to increase the excitation of the CNS and decrease down-regulation (dampening down messages from the brain) via the GABA neurotransmitter system. One of the changes observed is an increase in NGF messenger RNA (which codes for the neurotrophin, nerve growth factor). This is known as gene induction.

German author Zimmermann reported in 2001 ([118]), "Repeated or prolonged noxious stimulation and the persistent abnormal input following nerve injury activate a number of intracellular second messenger systems, implying phosphorylation by protein kinases, particularly protein kinase C (PKC). Intracellular signal cascades result in immediate early gene (IEG) induction which is considered as the overture of a widespread change in protein synthesis, a general basis for nervous system plasticity. Although these processes of increasing nervous system excitability may be considered as a strategy to compensate functional deficits following nerve injury, its by-product is widespread nervous system sensitization resulting in pain and hyperalgesia."

The pathophysiology of neuropathic pain involves:

- *Excitotoxicity:* One of the mechanisms now known to be responsible for the central sensitisation is the NMDA receptor output. This glutamate receptor switches a low level of peripheral input to a high level of neuronal activity. Once the NMDA receptor is recruited by repeated C fibre (sensory from the periphery) stimulation, there is a massive output for the same (maybe minimal) level of stimulation as before. When the stimulus is discontinued, there is a slow recovery to normal, baseline levels of NMDA. NMDA receptors are implicated in "wind-up", neurogenic inflammation, neuropathy and spinal ischaemia. Ketamine, at low doses, blocks NMDA receptors. Ketamine is a dissociative anaesthetic that is occasionally used for pain relief but unfortunately may cause side-

effects such as hallucinations, amnesia and motor deficits. Schwartzman and Maleki noted ([119]): "The role of the clinician in identifying and eliminating the source of the pain is crucial before the effects of excitotoxicity and central sensitization permanently alter the physiology of the central pain-projecting neurons and make treatment ineffectual." Glutamate has also been implicated in CNS inflammatory conditions. In an experimental model of Multiple Sclerosis, glutamate excitotoxicity was investigated ([120]): increased extracellular glutamate is important in damage to oligodendrocytes and axons. Activated immune cells present in the inflammatory infiltrates in CNS lesions produce cytotoxic factors such as tumor necrosis factor α ([121]), matrix metalloproteinases ([122]), active oxygen species ([123]) and autoantibodies ([124]), and may also kill by direct cell-to-cell contact. During inflammation, glutamate is produced and released into the extracellular space ([125]) by activated leukocytes and microglia. Increased glutamate levels have been found in the cerebrospinal fluid of patients with CNS inflammatory conditions, such as acute encephalitis, meningitis and MS ([126];[127]).

- *Sodium channels:* accumulation of sodium channels can occur at the neuroma site, at tips of injured axons, along the length of the axon and at the dorsal root ganglion and results in foci of hyperexcitability and ectopic discharges in the axon and the cell body of the injured neuron, causing episodes of stimulus-independent (spontaneous) pain. Therefore these sodium channels are the target for drug treatment with agents such as anticonvulsants and local anaesthetics.
- *Ectopic discharges:* "Injured afferent neurons produce spontaneous activity that is generated away from the normal impulse generation site... this activity, referred to as ectopic discharges, may play a significant role in neuropathic pain" ([128]) Data from rat studies suggest that there are two components of ectopic discharge generator mechanisms: sympathetically dependent and sympathetically independent.
- *Deafferentation:* due to partial or complete interruption of peripheral or central afferent neural activity. In 2000, German authors reported on a rat study of L5 spinal nerve injury: "After dorsal rhizotomy neuropathic pain behavior may be related to deafferentation whereas after spinal nerve lesion it may be caused by ectopic activity." ([129])
- *Central sensitisation:* "may be manifested as increases in spontaneous and stimulus-evoked neuronal activity within the spinal cord, which, in turn, contribute to the development and maintenance of neurogenic and inflammatory pain syndromes." ([130]) There may be an increase in spontaneous neural activity of pain transmission pathways (including dorsal horn neurons and pain-related thalamic neurons) resulting in spontaneous pain.
- *Sympathetic involvement:* Baron noted ([131]): "After nerve lesion the sympathetic nervous system might interact with afferent neurons. Activity in sympathetic fibers can induce further activity in sensitized nociceptors and, therefore, enhance pain and allodynia (sympathetically maintained pain). This pathologic interaction acts via noradrenaline released from sympathetic terminals and newly expressed receptors on the afferent neuron membrane."

Peripheral sensitisation:

In peripheral sensitisation, tissue damage, and inflammation, along with sympathetic nerve terminals, give rise to a 'sensitising soup' of chemicals such as prostaglandins, histamine, cytokines etc. These cause a lowered threshold of nociceptors, ectopic nerve discharges, and accumulation of sodium channels.

Central sensitisation:

Soon after a peripheral nerve injury, the dorsal horn is bombarded by a variety of neurotransmitters. Amongst these, glutamate and aspartate, which are excitatory transmitters, interact with the N-methyl-D-aspartate (NMDA) receptors and neurokinin interacts with the neurokinin type 1 (NK1) receptors. Hyperalgesia after tissue injury and inflammation may be due to prolonged and excessive activation of spinal cord excitatory amino acid receptors and subsequent intracellular cascades. Tonic activation of NMDA receptors activates second-messenger systems, resulting in sensitization of ion channel complexes, including that of the NMDA receptor. As a consequence, this leads to calcium entry into the cell.
Calcium acts as a very important secondary messenger, activating nitric oxide synthetase and thus resulting in the synthesis of nitric oxide. It leads to immediate early gene expression as well as activating phospholipases, which decrease the threshold of the dorsal horn and lead to ectopic discharges.
Luo et al. ([132]) investigated the upregulation of dorsal root ganglion ?$_2$d calcium channel subunit and its correlation with allodynia in spinal nerve-injured rats. They hypothesised that "nerve injury may result in altered ?$_2$d subunit expression in spinal cord and dorsal root ganglia (DRGs) and that this change may play a role in neuropathic pain processing."
The anticonvulsant drug Gabapentin only reacts with abnormal calcium channels and has been found to be useful to combat neuropathic pain and recently to have some effect on muscle spasms. Luo et al. noted that spinal injection of gabapentin suppresses allodynia by an unknown mechanism.

These central changes are initiated by abnormal input to the spinal cord, which, in turn, may result from peripheral nerve injury or tissue inflammation.
Potential peripheral generators of this input include nerve injury- induced impulse discharges, generation of ectopic nerve discharges, action potentials, aberrant sympathetic influences, and sensitisation of peripheral nociceptors ([133]). These are all features of peripheral sensitisation.

Central sensitisation or 'wind-up' is mediated by a number of neuromodulators, such as adenosine triphosphate (ATP), calcitonin gene-related peptide (CGRP), aspartate glutamate (NMDA), nerve growth factor (NGF), substance P, nitric oxide, neurokinin and eicosanoids (prostaglandins, thromboxanes, leukotrienes).
Thus these substances are appropriate targets to prevent central sensitization.
Immune cells (mast cells) are also involved in hyperalgesia, as they produce NGF, 5-HT and histamine. NGF is found in conditions such as interstitial cystitis. NGF introduced into the bladder experimentally, induces a protein called Fos in the spinal cord. Fos is a marker of persistent activation such as that seen in central sensitisation.

A new line of research is looking into the role of endocannabinoid receptors, which are present in the body. These respond to cannabis-related compounds and similar compounds within the body in much the same way as endogenous opioid receptors respond to opiates like morphine and endorphins, which are the body's equivalent substances. Cannabinoids reduce NGF-induced Fos expression.

Processing:

As stated before, pain is a subjective, conscious sensation, so it is obviously essential to look at which parts of the brain are involved.

Recently available imaging techniques such as PET and fMRI (functional MRI) scans have shown that there is no single pain centre but rather several areas that are activated by pain. The thalamus, limbic system and various cortical areas (inferior parieto-temporal, prefrontal, insular and anterior cingulate) are all involved.

It is likely that NMDA involves the limbic system, which is also responsible for the link between sensation, emotions and the endocrine (hormonal) system.

Laurent et al. ([134]) looked at PET and fMRI scans of brain function related to central pain. They noted the prior sixteen studies using PET had demonstrated pain-related activations in the thalamus, insula/SII, anterior cingulate and posterior parietal cortices. They also reported that activity in right pre-frontal and posterior parietal cortices, anterior cingulate and thalami can be modulated by attention (hypnosis, chronic pain, diversion, selective attention to pain) and therefore "probably subserve attentional processes rather than pain analysis."

The brain not only receives incoming information but also sends descending inhibitory messages to "dampen" the system. Descending inhibitory control from the thalamus is partly mediated within the brainstem in the periaqueductal grey. This system inhibits the transmission of phasic (short, sharp) pain more effectively than tonic (persistent) pain. The latter is probably inhibited within the mesolimbic dopamine system.

The main neurotransmitters involved with the descending control include:

- Serotonin (5-HT)
- Acetylcholine (Ach)
- Noradrenaline (alpha2 receptors)
- Gamma-aminobutyric acid (GABA)
- Endorphins (opioid receptors)
- Glycine
- Cholecystokinin (CKK)

Hence agents that affect these neurotransmitters are targets for pain treatment.

In summary, pain is initiated by nociceptors that detect damage. The message is transmitted via numerous neurotransmitters along neurones to the central nervous system (CNS). In the spinal cord, there may be a "sensitisation" which results in any descending control of pain (from the brain) being over-ridden. Pain is perceived in the brain and may affect a number of different parts of the brain, which has a bearing on other effects such as emotional, endocrine and immune. Descending control may modulate pain.

HOW DOES ARACHNOIDITIS CAUSE PAIN?

There are 2 principle ways in which the scar tissue of arachnoiditis causes pain at a local level. (Noting of course that there may well also be pre-existing or persisting underlying spinal pathology that contributes to the picture).

The first is mechanical: the physical effect of the scar on the tissue on which it impinges. This is broadly similar to the effect of a prolapsed disc. Nerve roots or dorsal root ganglia may be compressed. Nerve roots are commonly affected and the result will be sensory, causing pain and sensory disturbance, and motor, causing weakness and muscle spasms.

In rats, experimental compression of nerve roots by loose chromic gut ligatures induced prolonged Thermal hyperalgesia (related to neuropathic pain), and initial transient motor dysfunction and mechanical hypoalgesia ([135]).

Compression causes different effects depending upon the level of pressure exerted upon the affected nerve root. High pressure can directly deform nerve fibres and derange the integrity of the nerve structure, whereas low-pressure causes impaired blood supply, reduced nutritional transport and intraneural (inside the nerve) oedema, which is associated with intraneural fibrosis ([136]). Olmarker and Rydevik ([137]) demonstrated that cauda equina blood supply is interrupted by pressure equaling arterial blood pressure. 10mmHg applied pressure caused 20-30% reduction in nutrient transport to nerve roots. Additionally, pressure can change the permeability of endoneural capillaries giving rise to oedema.

Dorsal root ganglia are highly sensitive to compression; normal, non-injured DRG respond to gentle pressure by producing prolonged repetitive firing. (Howe et al. 1977[138]). Hanai et al. ([139]) more recently demonstrated that the DRG not the dorsal root, produced this response when either the root or the DRG were compressed. Chatani et al. ([140]) studying rats, found that DRG irritation generated thermal hyperalgesia. Sugawara et al. ([141]) found that hypoxia (lack of oxygen) further increased sensitivity to mechanical stimuli and even provoked spontaneous firing. As we have seen, adhesive arachnoiditis affects the flow of CSF and thus the provision of oxygen to nervous tissue within the affected area. Thus a lack of oxygen may compound the physical compressive effects of the scar tissue. Some authors (Lindblom & Rexed 1948[142], Rydevik *et al.*1984[143]) have suggested that the DRG is the most likely site of compression by prolapsed disc material.

Kuslich et al. ([144]) demonstrated that sciatica is produced by stimulation of a swollen, stretched, restricted (by scar tissue) or compressed nerve root. They concluded that the presence of scar tissue compounded pain associated with the nerve root by fixing it in one position thereby increasing its susceptibility to tension or compression.

Secondly, arachnoiditis may involve inflammation and it may be that the inflammatory mediators involved exert a chemical effect upon the nervous tissue. For instance, the inflammatory mediatorIL-1 plays an important role in experimental allergic radiculitis induced in rats, since IL-1 receptor antagonist ameliorated the symptoms (Wehling *et al.* 1996[145]). In fact, IL-1 and IFN act synergistically with TNF-alpha and are more or less neurotoxic (Chao *et al.* 1995[146]).
Peripheral nerve endings become sensitised by chemical mediators released during tissue damage and inflammation. These include neurogenic mediators, such as substance P, and non-neurogenic mediators, such as bradykinin, histamine and prostaglandins ([147]).
Histological damage may occur without compression (Anderson[148]), largely as a result of exposure to chemical irritants from sources such as the nucleus pulposus of herniated disc material. (See above). Inflammation renders the affected nociceptors more sensitive to mechanical stimulus such as that due to compression by scar tissue.

There may also be a third aspect of the effects arachnoiditis exerts both locally and more distantly. This relates to the impact on CSF flow. Various authors have postulated impaired CSF flow in the development of syrinx secondary to arachnoiditis, and Jenik et al. described arachnoiditis symptoms as predominantly "syringomyelic" in nature ([149]). Warnke et al. ([150]) recently published a paper in which they reported on findings at thecaloscopy. They noted that patients with a large thecal sac on MR and confirmed arachnoiditis at thecaloscopy had CSF under pressure. They also commented on patients who experienced some relief of symptoms after lumbar puncture, conjecturing that this was due to temporary reduction in CSF pressure and "alteration of venous filling". The authors noted that the subarachnoid space is not a single space but is divided by various arachnoid membranes, so that pressure levels may vary in different locations, and suggested: "We assume that long term disturbances of CSF circulation with raised local CSF pressure may dilate the thecal sac...it is our opinion that further investigation should be concentrated on the solution of the problem of lumbar intrathecal CSF flow disturbances."
The disturbed CSF flow may cause local effects, but also potentially more distant effects and could account for unexplained upper body symptoms in patients who have lumbosacral arachnoiditis but no evidence of pathology in thoracic or cervical regions.

Aside from nervous tissue being affected, other anatomical structures in the vicinity may also be sources of pain. These include prevertebral (intrinsic) muscles, ligaments (longitudinal, intertransverse etc.), joints (facet and zygopophyseal), dura, dural attachments, vertebral periosteum and epiradicular components. Innervation of these structures (ventral and dorsal rami, sinuvertebral nerve) may be affected if the

epidural space is compromised. Arachnoiditis is often accompanied by epidural fibrosis, so this may be a significant factor in generating pain.

In addition, sympathetic innervation may be affected (see below.)

Sensitisation of nociceptors in these tissues can, as we have seen, trigger a centralisation of the pain via the 'wind-up' process. This leads to a more widespread pain, which is commonly seen in arachnoiditis: central pain. (See below). In addition, loss of input from impaired nerves may trigger a compensatory upregulation of central receptors. Again, this effects a central sensitisation.

SUMMARY: clearly the picture in adhesive arachnoiditis is somewhat complex, broadly comprising the effect of a combination of mechanical and chemical factors on various structures in and around the thecal sac. These factors act somewhat synergistically to produce a sequence of events that are progressive and may lead on to centralisation of pain. Further discussion of central pain can be found below.

CAUSES

A. MECHANICAL:

- Spinal surgery (especially multiple)
- Multiple lumbar punctures
- Trauma
- Spinal stenosis
- Chronic disc prolapse

B. CHEMICAL:

- Myelographic dyes : oil-based(Iophendylate: Myodil/Pantopaque and water-based (various)
- Epidural steroid injections (e.g. Depo-Medrone)
- Epidural anaesthesia
- Other intraspinal drugs such as amphotericin B and methotrexate

C. MISCELLANEOUS:

- Infection e.g. meningitis
- Subarachnoid haemorrhage

In my Global survey, in 1999, I found that there were the following rates of risk factors:

1. Trauma: 8%

2. Stenosis: 18%
3. Spinal surgery: 75%
4. Dural tear/puncture/CSF leak: 3%
5. Spinal tumour: 1%
6. Lumbar puncture: 2%
7. Oil-based myelogram: 59% (40% oil-based only, 19% more than 1 myelogram dye)
8. Water-based myelogram: 29% (3% water-based only, others more than 1 dye)
9. Unspecified myelogram: 20%
10. Spinal/epidural anaesthetic: 18%
11. Epidural steroid injection: 61%
12. Chymopapain: 1%
13. Meningitis (including chemical): 7.5%
14. Subarachnoid Haemorrhage: 2 cases

NOTE: In the majority of cases, there were a number of risk factors rather than a single one. Many participants in the survey had complex histories.
There were only 7 out of 316 cases in which no chemical injection was involved, and 69 cases in which there was no history of spinal surgery.

There were a number of associated conditions:

1. Syringomyelia: 6 cases
2. Arachnoid cyst: 1
3. ACM1 (Arnold-Chiari Malformation Type1): 1
4. Pars defect: 1
5. Spina bifida occulta: 12
6. Tethered cord: 3
7. Spinal abscess: 2
8. Post-operative infection (spinal): 2
9. Tarlov cysts: 2

Other possible associated factors included:

1. Intraspinal narcotic (pump): 8 cases
2. Spinal cord stimulator: 7
3. Rhizolysis: 2

MECHANICAL CAUSES:

Post-traumatic arachnoiditis cases:

Ramli et al ([151]) described a case of Brown-Sequard syndrome that causes pain and sensory disturbance on one side of the body. The USA National Institute of Neurological Disorders and Stroke (NINDS) describes Brown-Sequard syndrome (BSS) as "a rare neurological condition characterized by a lesion in the spinal cord which results in weakness or paralysis (hemiparaplegia) on one side of the body and a loss of sensation (hemianesthesia) on the opposite side." BSS may be also caused by a spinal cord tumour, trauma ((e.g. puncture wound to the back/neck), ischaemia (restricted blood supply), infection (often viral) or inflammatory diseases such as tuberculosis, or multiple sclerosis)).

Usanov et al., at the Polenov Research Neurological Institute ([152]) described a case of post-traumatic cystic adhesive arachnoiditis of the thoracic region which presented a few months after the traumatic incident with weakness of the legs and episodes of periodic urinary incontinence, reduced sensation of the lower trunk and legs. MRI showed narrowing of the spinal cord at T8 with widening of the subarachnoid space at and around this level due to "a marked adhesive process"; there was also an arachnoid cyst at T9-10 and subarachnoid block at T7.

Familial spinal arachnoiditis:

Japanese authors Nagai et al. ([153]) reported 2 patients with familial spinal arachnoiditis, who both had spastic paraparesis and sensory disturbance from the thoracic level. MRI demonstrated extensive arachnoiditis including cystic structure, adhesion between the spinal cord and dura, deformation of the spinal cord and secondary syrinx formation.

Post-spinal stenosis:

Spinal stenosis is a term that means narrowing of the spinal canal or the nerve root foramina. It is thus divided into central or lateral stenosis. Central stenosis produces compression of the thecal sac: soft tissue (ligamentum flavum and disc) may contribute as much as 40% to this compression.
It is more common in males because their spinal canal is smaller at the L3-L5 level.
Lateral stenosis involves impingement of nerve roots lateral to the thecal sac, as they pass through the neural foramina. It is made worse with hypertrophy (overgrowth) of the ligamentum flavum and /or joint capsule. Foraminal stenosis affects the exiting (upper) nerve root.
Compression of neural structures produces root ischemia and stenosis also compresses vascular supply of nerves so that symptoms are predominately those of neural ischemia. (Inadequate blood supply to nerves)

There are many different causes of stenosis, the commonest of which is degenerative changes in the spine. This is also referred to as spondylosis, and tends to occur in the older age groups.

However, there are other causes, including congenital or developmental stenosis. This presents at a much earlier age.

A further cause is spondylolisthesis, which is slippage of one vertebra on another, usually caused by degenerative problems or trauma. Stenosis may be post-traumatic or post-surgical.

Stenosis can occur at any level in the spine, but most commonly in the lumbar region. It is the commonest cause of Failed Back Surgery Syndrome (FBSS). Lumbar stenosis is a condition that progresses slowly, and has few clinical signs, thus often delaying diagnosis. Diagnosis relies mostly on symptomatology raising the possibility of the condition, thereby suggesting relevant investigations. "Symptoms are often chronic, frequently missed, or misdiagnosed in the medical community, and may cause severe disability or reduction in the quality of life."([154])

Epstein et al. ([155]) reported on 5 cases in which there was total obliteration of the subarachnoid space. 2 patients had stenosis and spondyloarthropathy, 1 had degenerative spondylolisthesis, 1 had previous spinal fusion and 1 had a large extruded disc. At laminectomy, "non-pulsating, thickened dural sac that conformed to the internal configuration of the involved spinal canal" was found.

Japanese authors Kawauchi, Yone and Sakou ([156]) used a myeloscope to assess the effect of arachnoiditis, present preoperatively, on the outcome for surgical treatment of spinal stenosis. In 36 patients with lumbar spinal stenosis, they found all had "various degrees of adhesive changes in the cauda equina". Patients with marked adhesions went on to do badly at operation and the authors concluded that, "Adhesive arachnoiditis was considered to be one of the causes for the poor operative results for LSS".

Razak, Ong and Hyzan in Malaysia ([157]), looked at the surgical outcome for lumbar spinal stenosis. They found that 4 out of 25 cases had recurrent symptoms such as claudication. One of these was due to arachnoiditis.

Jackson and Isherwood ([158]) looked at 165 patients with symptoms suggestive of degenerative lumbar spine disease. On MRI, they found central clumping of nerve roots in 16 patients (9.7%) associated with spinal stenosis at one of the affected levels in all. 44 patients had spinal stenosis. Nerve root clumping occurred in association with pure spinal stenosis (10 cases), stenosis secondary to disc prolapse (4 cases) and degenerative spondylolisthesis (2 cases). Clumping was confined to one vertebral level in 9 cases and extended 2-4 levels in 7 cases, of 5 which, spinal stenosis was present at multiple levels. The appearance of nerve root clumping was "indistinguishable" from that seen in adhesive lumbar arachnoiditis.

The authors concluded: "Abnormal central clumping of nerve roots as described in arachnoiditis may occur in association with spinal stenosis in the absence of other risk factors although the cause for this appearance remains unexplained. Arachnoiditis-like changes extending over more than one vertebral level are rare (7%) except in the presence of spinal stenosis at multiple levels (29%)."

Another important point to consider is that invasive techniques such as myelograms or epidurals will be entering an already compromised space and this may increase the risk of complications, of which arachnoiditis is one. Some of the studies done on post-myelographic arachnoiditis suggest that stenosis is a factor in the degree of severity. ([159])

POST-SURGICAL ARACHNOIDITIS

"Adhesive arachnoiditis with epidural fibrosis is the most common anatomic diagnosis associated with the syndrome called "failed back"."...The frequency of symptomatic epidural and/or arachnoid scarring following lumbar laminectomy ("failed back syndrome") is high -- affecting probably as many as 15% of patients." ([160])

The nerve roots lying within the dural sac are vulnerable to damage during surgery as a result of traction on them that irritates them causing inflammation which may lead to scar formation. The more the nervous tissue is disturbed at operation, the greater the risk. In addition, any blood entering the spinal fluid has a potential to cause inflammation; infection is another risk factor.

There may be some months' delay between the operation and the onset of symptoms, whilst the scar tissue develops to a clinically significant degree. Indeed, one might expect as much as 18 months of remission before recurrence of symptoms. Gradually increasing symptoms beginning a year or so after operation may represent scar radiculopathy. As the blood supply to the nerve roots is increasingly impaired, neurophysiological compromise results in pain and other neurological symptoms.

In 1946, French ([161]) described 13 cases of post-surgical spinal arachnoiditis; whilst Smolik and Nash in 1951([162]) also drew attention to this problem.

Burton et al ([163]), in 1981, cited 6-16% of all Failed Back Surgery Syndrome (FBSS) patients as having arachnoiditis as the *primary* pathologic process. Indeed, the authors suggest that adhesive arachnoiditis is "found to some degree in almost all FBSS patients." Note that of FBSS is seen in some 5-40% of spinal surgery cases.

In 1988, Cechini et al. ([164]) looked at 128 patients using post-operative CT scan. They found epidural fibrosis in 81%, spinal canal stenosis in 29%, calcification in 9%, dural sac deformity in 58% and pseudomeningocele in 4%. However, in the absence of a myelogram, they were unable to demonstrate intradural lesions. However, as Aldrete points out in his chapter on spinal surgical intervention, intrathecal calcification and dural deformity are suggestive of arachnoiditis.

Matsui et al. ([165]) conducted a serial post-operative MRI study in 10 patients to assess the effects of laminectomy on patients with prolapsed disc or stenosis. They performed axial MRI before and then 3, 7, 21 and 42 days after surgery. They found "Cauda equina adhesions were most severe at the laminectomised levels L3-4, L4-5 and L5-S1 (n = 16); partial adhesions were found in 9 of 16 levels at 6 weeks after surgery. At the L3-4 or L5-S1 levels (n = 14), the area of laminar exposure without laminectomy, the cauda equina adhesions continued 1 week after surgery, but thereafter resolved; only partial adhesions were seen at 5 of 14 levels 6 weeks after surgery. Shrinkage of the arachnoid sac was also found at the level of the laminectomy, but it re-expanded 3 weeks after surgery in all cases." The authors suggested that the adhesions and sac shrinkage were related to "an inflammatory process of deep

wound healing" that might explain "laminectomy-induced arachnoradiculitis" causing post-operative recurrent symptoms.

Wang et al ([166]) reviewed cases of dural tear secondary to lumbar spinal operations. They looked at 641 consecutive patients in a 5 year period and found that 88 (14%) sustained a dural tear, which was repaired during the operation. Longer-term follow-up showed that only 12 of these patients had a poor result with some residual back pain. One patient had arachnoiditis. The authors concluded that a dural tear did not significantly increase the risk of long-term deleterious effects.
Ozgen et al. ([167]), in 1999, looked at 114 patients with prior lumbar disc surgery who underwent a re-exploration for intractable back and/or leg pain. Adhesive arachnoiditis was found in 4 cases (3.5%); whereas 78% had disc herniation, 12.2% had epidural fibrosis, 3.5% had iatrogenic instability and 2.6% had spinal stenosis.

Chen et al. ([168]) looked at cases of posterior lumbar interbody fusion using implanted fusion cages (Bagby and Kuslich), publishing their results earlier this year. They found a "relatively high incidence of complications"; including 1.7% arachnoiditis (2 out of 118 patients) and 2.5% nerve injury (3 patients).

Recently Turkish authors Kayaoglu et al. ([169]) reported on a retrospective study of 85 patients undergoing re-operation after lumbar disc surgery. They found "recurrent herniation (20%), epidural fibrosis alone (36.4%), small recurrent herniation with epidural fibrosis (28.2%), herniation at another level (10.6%), spinal stenosis (2.4%), lumbar pseudomeningocele (1.2%) and adhesive arachnoiditis (1.2%)."

Surgery to correct spina bifida (myelomeningocele) carries a high risk of arachnoiditis and cord tethering (see below).

Muslin-induced arachnoiditis

This was first reported in 1978 ([170]) and only about 25 further cases can be found in the medical literature. About 90% of these involved women who have brain aneurysms in particular of the anterior communicating artery. Surgery on these aneurysms may include reinforcement of the aneurysm wall if it is thought to be unsuitable for clipping. Muslin reinforcement has been used since the late 1950s. This requires wrapping or coating the aneurysm in materials such as cotton gauze (muslin). This foreign material may induce a granulomatous reaction known as a 'muslinoma' or 'gauzoma'. Adhesive arachnoiditis is usually optochiasmatic. Brochert et al. ([171]) recently described a case in a 64 year old man. They noted that optic neuropathy in cases like this tends to develop secondary to the inflammatory process, causing visual loss beginning 1-24 months after surgery (longer delay may occur).

Arachnoiditis due to chronic disc prolapse:

Haughton et al. ([172]) postulated that disc contents leaking out through a torn annulus may have an inflammatory effect. They found that the contents of the central part of the disc, the nucleus pulposus, chondroitin (a component of the disc) and lactic acid produced by processes within the disc could cause inflammation, as could synovial fluid from degenerating facet joints. Looking at monkeys, the team found that nucleus pulposus produced "significant fibrosis in the arachnoid and epidural spaces." The authors therefore suggested that this was a factor in the inflammatory response. Saal ([173]) described the high levels of the inflammatory enzyme phospholipase A2 present in herniated or degenerating discs and the consequent discogenic pain.

Goupille et al. in 1998 ([174]) suggested that involvement of inflammatory mediators in causing radiculopathy had yet be proven, but suggested a hypothesis that leakage of inflammatory agents such as prostaglandins and interleukins may produce an excitation of nociceptors, a direct neural injury, nerve inflammation or enhancement of sensitisation to other pain-producing substances (such as bradykinin). Although these authors believe this effect to be transitory as a part of the early stage of disc herniation, it seems quite feasible that these inflammatory processes may in susceptible individuals become prolonged and progress to chronic problems.

It may be that, as Frank and Mayfield suggested ([175]) the immune capabilities of the arachnoid membrane, which were demonstrated in vitro, are responsible for initiating and maintaining an inflammatory response to the presence of disc material.

Miscellaneous associated mechanical spinal conditions:

1. <u>Split spinal cord malformations (congenital)</u>

Ersahin et al. ([176]) reviewed 74 cases. They noted spinal arachnoiditis "caused by the contrast material used in myelography" in two patients, who had paraparesis.

More recently, Iskandar et al. ([177]) looked at 20 myelomeningocele patients who had a split cord malformation (who comprised about 6% of all their myelomeningocele patients). The authors noted that all 15 patients who had a delayed diagnosis (mean age 4.4 years) "as expected" had arachnoiditis secondary to prior myelomeningocele repair. There was also evidence of tethering at the level of the split cord malformation.

Myelomeningocele (spina bifida) arises as a result of embryonic failure of neural tube closure, during the fourth week of gestation. This causes a protrusion of the meninges through a midline bony defect of the spine, forming a sac containing CSF. Usually MMC is associated with other malformations such as Chiari II, of the hindbrain. Before neurosurgical techniques came into use, there was extremely high mortality due to hydrocephalus or meningitis etc.

Surgical repair of the defect aims to prevent CSF leak, infection and subsequent spinal cord tethering, as well as preserving neurological function

Wagner et al. ([178]) described the consequences of primary myelomeningocele closure. They noted: "As primary

MMC repair is inevitably followed by the development of arachnoiditis, fibrosis and adhesions between intraspinal structures, MMC closure predisposes to secondary tethering of the cord."

They suggested that about a third of patients with MMC develop a symptomatic spinal cord tethering, which tends to present clinically as a progressive scoliosis, gait changes, spasticity or pain and sometimes with weakness, lower limb contractures and bladder dysfunction. Wagner and his colleagues noted that upper limb symptoms might also arise due to traction on the cervical cord.

Whilst the majority of patients may gain some remission of symptoms by undergoing surgery, later recurrence is likely.

Wagner et al. also remarked, "The subarachnoid spaces around the spinal cord regularly develop marked arachnoid adhesions after primary MMC closure." This may lead to arachnoid cyst formation in both children and adults.

2. Idiopathic spinal cord herniation: Berbel et al. ([179]) described a case of a man who underwent laminectomy for spinal canal stenosis, which did not successfully remove his symptoms. His presentation mimicked that of Brown-Sequard syndrome. MRI demonstrated ventral displacement of the thoracic spinal cord associated with an arachnoid cyst. At operation, the cyst was removed but attempts to free the spinal cord were unsuccessful due to severe spinal arachnoiditis. The authors suggested that whilst herniation of the cord is rare, that patients tend to present in a similar manner, with a gait disorder resembling that in Brown-Sequard syndrome.

3. Arachnoid telangiectasis: Buxton et al, ([180]) described a case of syringomyelia secondary to arachnoiditis arising as a result of arachnoid telangiectasia. The patient had no other signs of hereditary telangiectasia.

4. Spinal dermal sinuses

In September 2003, Ackerman and Menezes ([181]) published a paper on 28 cases of spinal congenital dermal sinuses, in which they reported 22 tethered cords, 14 inclusion tumors, and 6 patients with evidence of arachnoiditis. The authors remarked: "Although most patients were referred for cutaneous stigmata evaluation, >50% had neurologic deficit, intradural tumors, or tethered cords."

Hide Bound Cord

This phenomenon was described by Moquin and others in the United States, who have also coined the term thoracic cord syndrome.

Hide Bound Cord is a transient severe stretching of the spinal cord over a defect in the thoracic spine when the patient bends (even at rest if severe). It is associated with ischaemia or vasogenic congestion and microscopic injury. There may also be a syrinx. The defect is typically at the thoracic kyphus (T6-8) or within 2 levels above or below.

Radiographically there may be an exaggerated kyphosis and/or small disc herniations /spondylotic bars at the apex of the kyphosis. The spinal cord is in an anterior, fixed position resulting in draping across the

defect.

Moquin et al. postulated ([182]) that there is a relative tethering of the cord leading to a "Hide bound" appearance on MRI, with thinned/ deformed cord, loss of signal anterior to the cord as the cord is closely applied to the kyphosis. There may be syrinx above or below this area and abnormal cord movement on cord motility studies.

Patients tend to present with local thoracic pain, radiating band-like chest pain (uni- or bilateral), neurogenic claudication, constipation, bladder dysfunction, abnormal sensory perception (not necessarily within dermatomal limits), clumsiness/tripping, abnormal balance (especially falling in the dark etc.).

Maliszewski et al. ([183]) described tethered cord syndrome in adults. They presented 3 cases that developed adhesions of the spinal cord at a late stage after previous spinal interventions (trauma/surgery); symptoms appeared to have been precipitated by sudden stretching of the spinal cord due to a fall or strenuous exercise. In all 3, the posterior surface of the cord adhered to the dura at the site of injury. MRI findings were confirmed at operation. The authors remarked:

"The tethering of the cord by the scar was the cause of a non-physiological stretching of the spinal cord on flexion of the body and head. It led to spinal circulation disorders and symptoms of myelopathy."

CHEMICAL CAUSES OF ARACHNOIDITIS

"I know that most men can seldom accept even the most obvious truth if it would oblige them to admit the falsity of conclusions which they proudly taught to others, and which they have woven, thread by thread, into the fabric of their lives." Leo Tolstoy

As Rachel Carson wrote: "if having endured much, we at last asserted our 'right to know' and if, knowing, we have concluded that we are being asked to take senseless and frightening risks, then we should no longer accept the counsel of those who tell us that we must fill our world with poisonous chemicals, we should look around and see what other course is open to us."

It is recognised that arachnoiditis most commonly arises from medical procedures such as surgery, myelograms and epidural injections. Data on the incidence of clinically significant chemically-induced adhesive arachnoiditis has not, to date been available.

When it was originally described over 100 years ago, adhesive arachnoiditis was predominantly a disease of the thoracic spine due to infections such as tuberculosis. Nowadays it is most common in the lumbar region, and also seen in the cervical region, whereas thoracic arachnoiditis has become uncommon. This trend results from the influence of iatrogenic causes.

Surgery tends to cause localised arachnoiditis, whereas chemical insults such as myelograms and epidural injections give rise to a more diffuse picture, due to their spread along the cerebrospinal axis.

Aldrete includes in his book "Arachnoiditis: The Silent Epidemic" a brief recap on the causative factors, shown in a small table, with percentage figures for each factor. He has drawn these figures from what he describes as "a systematic and careful anamnesis" involving 162 patients.
3.7% of the cases were due to a myelogram performed before 1986 (i.e. inferred as using oil-based dye) whilst 16% resulted from a combination of myelogram and spinal surgery. 27% resulted from laminectomy, with a further 16%, 10% and 19% for other surgical techniques.
3.7% of his cases involved spinal anaesthesia with 5% lidocaine, with 1.8% due to "epidural anaesthesia with documented parasthesia". Epidural blood patch was the causative factor in a further 1.8% of the patients.

In 1999, Dr. Charles Burton, Director of the Institute for Low Back and Neck care in Minnesota, wrote a paper entitled: "The Subarachnoid Space: 'Salum Sanctorum' or Toxic Dump?"([1841])
He describes the subarachnoid space as a "very delicate and fragile structure", "The true 'salum sanctorum' of the human body" and states, "This fragility allows only a slight tolerance for insult."

This concurs with Oldberg's statement in his 1940 paper ([185]), (entitled "A Plea for Respect for Tissues of the Central Nervous System"):"Certainly to inject a substance like alcohol directly into the spinal fluid, with the attendant risk to conus, cauda and arachnoid, should be regarded as a major clinical decision. One wonders what will happen to these structures in ensuing years, when the inevitable fibrosis initiated by incautious and unwarranted injections progresses."

Burton goes on to state:
"The adverse sequelae relating to the introduction of foreign body substances into the body's 'salum sanctorum' remains a game of chance for the patient."

As Aldrete has explained in his recently published book**,** "Arachnoiditis, The Silent Epidemic", the subarachnoid space appears to be particularly vulnerable to toxicity because of the baricity of the substances injected, the slow rate of their removal from the spinal fluid into the bloodstream (part of the reason why intrathecal morphine is regarded as advantageous to systemic administration as side-effects such as sedation and nausea are reduced), the closed compartment is constrictive and may allow "greater loculation and fixation of some of these substances", and lastly, the circulation rate of the CSF is relatively slow.

HISTORICAL PERSPECTIVE

The introduction of myelograms in the early twentieth century heralded an upsurge in severe diffuse adhesive arachnoiditis. Air was first used for myelography, and then Thorotrast was used, which was highly toxic due to its radioactive nature. No-one knows how many people were damaged by it, but the numbers were undoubtedly in the thousands.

Oil-based contrast agents such as Myodil (Pantopaque) were introduced after very cursory pre-clinical trials in the early 1940s, despite the animal studies repeatedly demonstrating severe damage to nervous tissue ([186]; [187];[188]); they were toxic and caused significant adverse effects as frequently as 74% of cases ([189]). These included nerve damage and even demyelination.

An article by Dr. H. L. Feffer, in Medical World News in September, 1978 entitled Arachnoiditis Risk After Myelography, suggested that the at least a quarter of patients undergoing a myelogram (400,000 then being performed every year in the US) develop iophendylate arachnoiditis and furthermore, that those undergoing two or more myelogram studies have a 50% chance of developing iatrogenic arachnoiditis. Dr. Feffer cited imprecise technique, retention of dye and emulsification of the dye with blood, and stated that animal studies confirm "the devastating effect of iophendylate on the myelin sheath and nerve cells as well as the meninges and nerve roots."

Over the ensuing 40 years of use, cases of clinically significant adhesive arachnoiditis have also been well documented by many authors ([190];[191];[192]). In 1980, William H. Strain, who was instrumental in developing the clinical use of iophendylate, stated that "millions" of iophendylate myelograms had been performed since its first use in 1942. He admitted that reactions from the use of his contrast agent were well known, reporting that arachnoiditis may exist in 10-15% of patients who had been investigated with myelography ([193])

In 1962, Mason and Raaf ([194]) reported a case of obliteration of the subarachnoid space by Pantopaque arachnoiditis. Postmortem findings in the patient, who died seven months after myelography, showed retention of 4ml of dye within the subarachnoid space, complete obliteration of the space with a membrane 1-10mm thick, extensive vacuolisation throughout the outer two-thirds of the spinal cord and parts of the cerebral hemispheres.

The risk of serious adverse effects increases substantially if more than one myelogram is undertaken. Many authors suggested that it was a combination of the dye and blood in the subarachnoid space (usually during surgery) that caused arachnoiditis, but animal studies showed that the dye alone could be responsible ([195]).

Controversy raged for some time over the issue of aspiration of the dye. However, evidence suggested that even with diligent attempts to remove the dye, some residual inevitably remained, causing a toxic reaction ([196]; [197]; [198]; [199]). Bergeron et al. ([200]) noted in their monkey study, that there was always some reaction with retained Pantopaque and that therefore as much dye as possible should be removed after the examination.

Iophendylate persists within the central nervous system, particularly in the basal cisterns and the lumbosacral region, as either encapsulated droplets (195), which may calcify, or a thin film ([201]; [202]; [203]). The

former can be easily detected on standard X-rays but the latter may be virtually invisible, even on MRI, or misinterpreted as a layer of fat, which it tends to resemble. It may be that the encapsulated residual dye exerts mass effects locally, or if trauma disrupts the cysts, the dye can escape and cause a chemical inflammation. The thin film would be more likely to cause a diffuse reaction and possibly a systemic toxic reaction.

Residual dye has been implicated in causing chronic headaches ([204]) and focal seizures ([205]).

Doctors in Sweden were quick to recognise the toxicity of iophendylate and discontinued its use by the 1950s. However, it was still in use in the UK (as Myodil) and around the world until the late 1980s.

In time, water-soluble agents such as Dimer X and Conray replaced Pantopaque. The early water-soluble dyes were still capable of serious and lasting side-effects ([206]). Metrizamide (Amipaque) is particularly linked with risk of seizures and neuropsychiatric disturbance ([207]). Later dyes also carried a risk of arachnoiditis, especially if given in too high a concentration or too large a dose. There have been cases of chemical meningitis caused by water-based myelogram dyes; this may later develop into adhesive arachnoiditis.

Solanki ([208]) cites Naylor's 1962 paper suggesting a chemical or autoimmune process may be responsible for neurological damage in arachnoiditis due to contrast media as evidence in favour of a chemical and immunological neuritis.

Iopamidol was introduced in Italy and in Germany in 1981 as the first commercially available non-ionic water-soluble contrast medium approved for myelography. Since then more than 110 million units have been sold worldwide and some 3,000 scientific publications pertaining to its use have been published. Nevertheless, the manufacturers have issued the following warnings:

1997

Bracco Diagnostics, Inc. USA and Italy

IOPAMIDOL *INJECTION, USP*

NOT FOR INTRATHECAL USE

WARNINGS:

Severe Adverse Events - Inadvertent Intrathecal Administration

Serious adverse reactions have been reported due to the inadvertent intrathecal administration of iodinated contrast media that are not indicated for intrathecal use. These serious adverse reactions include: death, convulsions, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, seizures, rhabdomyolysis, hyperthermia, and brain edema. **Special attention must be given to insure that this drug product is not inadvertently administered intrathecally.**

Source ([209])

In 1997, H.R. 738 was introduced as a Bill in the US House of Representatives, concerning "Myelogram-Related Arachnoiditis Amendments" calling for discontinuance of the use of Pantopaque, Amipaque, Omnipaque and Isovue.

Preservatives in Spinal Injections

In 1955, Hurst conducted studies on monkeys ([210]), which demonstrated that a wide range of chemicals, when introduced into the CSF, produced an immediate pathological response, which "proceeds steadily to its termination". The early stages are asymptomatic, but after a latent period, the clinical picture is then one of "severe and progressive signs and symptoms". This is similar to the picture in arachnoiditis, and therefore all short-term studies (which make up the majority of the evidence concerning safety of ESI*) will fail to address the issue of arachnoiditis, which tends to occur after an indeterminate interval following exposure.

* Epidural steroid injection

In 1975, Kelly et al ([211]) wrote a paper describing the neuropathological effects of intrathecal water. They concluded that infusion of distilled water intrathecally could cause distinctive lesions of spinal roots and cord. It follows therefore, that if a substance as inert as water can cause damage, that more complex preparations are likely to carry some risk also.

As early as 1954, Moore ([212]) advised that local anaesthetic administered epidurally should be free of preservatives. Malinovsky ([213]) suggests that "neurotoxicity can result from …the use of adjuvants." Some authors suggest that arachnoiditis occurs as a result of the vasoconstrictive component of the anaesthetic, whilst others say that contaminants ([214]) or preservative agents are responsible.

It must be stressed that ANY drug preparation injected in to the spine, may contain preservatives such as benzyl alcohol, polyethylene glycol, and chlorobutanol (a derivative of chloroform) and that these carry a risk of neurotoxic effects. Another preservative that can cause reaction is sodium bisulfate, which may trigger a severe allergic reaction if the patient is susceptible (and it is unclear how many of the general population may be susceptible).

Ketamine, which is used in anaesthesia, is administered in solutions that commonly contain preservatives such as chlorobutanol, a derivative of chloroform, which has been implicated as causing neurotoxicity in animal studies when injected intrathecally. Indeed Malinovsky et al ([215]) describe "significant severe spinal cord lesions" at concentrations of 0.05% chlorobutanol.

Usually the injectable form of morphine sulfate contains 0.5% chlorobutanol and not more than 1% sodium bisulfate in every ml of morphine sulfate injection USP. An animal study in 1993 showed that 0.05% chlorobutanol injected intrathecally "induced significant severe spinal cord lesions" ([216]). It is therefore vital to ensure that preservative-free solution is used. Chlorobutanol toxicity may cause increased somnolence, alterations in speech patterns, dysarthria and haemodynamic changes. ([217])

Hetherington and Dooley ([218]) noted in 2000 that the intrathecal route of administration "reduces systemic adverse effects, but can increase the risk of local adverse effects such as arachnoiditis."
They also remarked "It is accepted practice that any spinal injection should not contain any preservatives (such as benzyl alcohol and parabens-containing compounds). The intrathecal administration of solutions preserved with benzyl alcohol has been shown in case studies to increase the risk of adverse neurological events... Steps should be taken to ensure that preservative-free products are used."

Recently in America, a journalist reported ([219]) on adverse events due to implanted morphine pumps: 8 of 13 patients at a Memphis, Tennessee pain clinic suffered severe neurological problems after a pharmacist apparently made faulty batches of morphine from bulk ingredients to refill their pumps. Three of the eight required surgery and are now partially paralysed. An investigation by the Tennessee Board of Pharmacy found two jars of compounded solution containing a mixture of morphine and methadone but labelled as morphine. Contaminants ethanol and methanol were also found in poor quality morphine powder. Compounded preparations used for refills from bulk, unsterile powders may carry a risk of contamination not only from processing chemicals, but also from organic debris that can slip through filters designed to strain out bacteria. Pharmacist Sarah Sellers, who is a consultant to an FDA advisory committee on pharmacy compounding, is highly critical of using compounded drugs
to fill implantable pumps. This again demonstrates the dangers of impure preparations when placed into the spinal fluid.

Radiologists in Minneapolis, when faced in 2001 with a shortage of Celestone Soluspan, a preservative-free steroid preparation which they used for epidural injections, issued a statement to all referring physicians: "As you may know, the inadvertent injection of Depo-Medrol and other members of the steroid family into the thecal sac can cause arachnoiditis. This is a risk and complication which we feel is unacceptable and will therefore not use Depo-Medrol as a substitute."
By doing so, this group (Consulting Radiologists Ltd.) demonstrated their commitment to avoiding the use of preservatives. Physicians throughout the world should follow this example.

Epidural Steroid Injections (ESIs)

Introduction

Mulligan and Rowlingson ([220]) in 2001 remarked: "Although possessing a long history of use, the therapeutic use of epidural steroid injections still needs substantiation."

How they are performed:

Cervical, thoracic, and lumbar epidural injections can be approached through translaminar (interlaminar) and transforaminal injections.
The translaminar approach is in the midline or paramedian and requires the needle to penetrate skin, subcutaneous tissue, paraspinal muscles (paramedian approach) or interspinous ligament (midline approach), and ligamentum flavum. The needle is advanced in an oblique approach until its tip touches the

posterior lateral portion of the vertebral body, located superior to the intervertebral foramen just under the pedicle. (See diagrams)

The transforaminal approach is performed by placing the needle in the neuroforamen (hole) ventral (anterior) to the nerve root.

In addition, there is a third possible approach for lumbar injections: caudal. This involves inserting the needle through the sacral hiatus into the epidural space at the sacral canal.

Bevacqua, Haas and Brand ([221]) investigated the depth of the posterior epidural space (ES). They found: "The posterior ES has been found to be somewhat larger and more variable than previously described. The findings provide clinical confirmation of recent radiologic and cadaveric studies, which portray a posterior ES of variable size and complex shape. These findings have implications for cannulation and use of epidural therapy as well as for the combined catheter epidural and single-dose spinal technique." This emphasises the considerable variation between individuals, which makes accurate placement of drugs more difficult.

In patients who have had previous spinal surgery, there may be scarring in the epidural space which further confounds accuracy of needle siting.

Mechanism of action:

Lee et al. ([222]) looked at the effects of steroids on prostaglandin phospholipase A2 in an animal model. It is thought that some disc-related pain is due to inflammatory mediators such as this phospholipase. They found that the level of phospholipase A2 activity was at its maximum at 1 week after surgery in group I (saline injection, loose ligature of nerve root surgery) and group IV (betamethasone 3 days after surgery). It showed a steady reduction in the steroid group, whereas it remained relatively high and dropped rapidly after 3 weeks in the saline-treated group, and returned to the level of a normal nerve root at 6 weeks after surgery. They suggested that the irritated nerve root was caused in part by a high level of phospholipase A2 activity initiated by inflammation, and that the mechanism of action of epidural steroid injection is inhibition of phospholipase A2 activity. The other steroid groups (II and III) were given betamethasone 0.1 ml a day before surgery (II), or a day after (III). There was no significant difference in recovery time among steroid injection groups.

Epidural steroid injections are administered in an attempt to reduce inflammation of affected nerve roots. Slucky et al. ([223]), in their dog study, were unable to demonstrate any material effect of the steroid on the dura on the collagen matrix, although they did see a significant decrease in the number of intracytoplasmic mitochondria (cell energy generators) of dural fibroblasts in steroid-injected animals, suggesting a metabolic inhibitory effect.

Abram stated ([224]): "Radiculopathy following disc herniation appears to be produced by either mechanical or chemical nerve root inflammation. Epidurally injected corticosteroids most likely exert a beneficial effect through anti-inflammatory rather than direct analgesic mechanisms."

Types of approach:

Carrino et al. ([225]) looked at spinal steroid injections in the US from 1993-1999. They found that "Despite an overall increase in spinal injection procedure volume and reimbursement... nonradiologists performed most of these procedures. Epidural steroid and facet joint injections had the highest volume and reimbursement ... and were performed almost exclusively by nonradiologists (predominantly anesthesiologists)."

Cluff et al, at Massachusetts General Hospital, Boston, ([226]) looked at practice of epidural steroid injection across the United States. They noted: "it is not clear whether there is consensus on their technical aspects. The current literature suggests that variations in technical aspects may affect ESI outcomes." They found that private practices use significantly more fluoroscopy than academic centres, especially with cervical injections (73% of private practices compared with only 39% of academic institutions polled use fluoroscopic guidance). After laminectomy 61% of private practices, but only 15% of academic centres, use the transforaminal approach. They concluded that there remains no consensus as to treatment and practice still varies widely.

Price et al. ([227]) compared caudal and lumbar approaches.93% of lumbar and 64% of caudal epidural injections were correctly placed. 97% of lumbar and 85% of caudal epidural injections, which were clinically judged as being correctly placed, were confirmed radiographically. In those where clinical judgement was uncertain ("maybe"), 91% of lumbar injections, but only 45% of caudal injections were found to actually correctly placed. The authors suggested, "In the non-obese patient, lumbar epidural injections can be accurately placed without x ray screening, but caudal epidural injections, to be placed accurately, require x ray screening no matter what the weight of the patient."

Chen and Foye in an online article on epidural steroids updated in March 2002 ([228]) noted that epidural injections using a caudal approach were first performed in 1901 when cocaine was injected to treat lumbago and sciatica. In the 1920s-40s high volumes of normal saline and local anesthetics were used. Epidural corticosteroid injection as part of the conservative (non-surgical) management of lumbar radicular pain was first recorded in 1952.

The most commonly used steroid compounds include betamethasone sodium phosphate and betamethasone acetate (Celestone Soluspan), methylprednisolone acetate (Depo-Medrol), and triamcinolone hexacetonide (Aristospan).

Each millilitre of Celestone Soluspan contains 3 mg of highly soluble betamethasone sodium and 3 mg of the relatively insoluble acetate salt. Thus, Celestone Soluspan provides both rapid onset and extended anti-inflammatory activity.

Depo-Medrol and Aristospan, in contrast, being relatively insoluble, provide a sustained anti-inflammatory effect.

As Chen and Foye pointed out, as injected methylprednisolone remains in situ for approximately 2 weeks, there should be a 2 week delay after the injection before assessment of the patient's response and administration of a repeat injection. This interval could be shorter, if an alternative short-acting steroid were used.

Debi et al. ([229]), in Israel, reported on a technique of applying 80 mg methylprednisolone acetate (Depomedrol) or the same amount (2 mL) of saline, soaked in 2.5 x 2.5 cm of collagen absorbable haemostat (Instat) that was left on the decompressed nerve root after lumbar laminectomy. At 1 year post-op, no difference in outcome was reported. However, one should note that here again is a potential for arachnoiditis, with increased exposure time and a foreign body which could trigger an inflammatory reaction and hence, arachnoiditis.

Fluoroscopy

Fluoroscopy is rather like the X-ray equivalent of a camcorder compared with a camera; instead of a static picture, there is a dynamic film from a continuous X-ray beam, transmitted to a monitor screen so that the doctor can observe the progress of the procedure.

It is used in various procedures, including cardiac catheterisation, barium studies etc.

Some authors advocate the use of fluoroscopy to ensure correct placement of epidural steroid injections. However, others point out that it is only with use of contrast agent that one can be sure not to have hit a blood vessel.

"As mentioned previously, reports suggest that injection without fluoroscopic guidance (i.e., blind injection) result in 30-40% of needle misplacement, including needle tip placement outside the epidural space (e.g., intravascular injection) and not at presumed level of pathological process. Therefore, although it is not a standard, it is recommended that ESIs be performed under fluoroscopic guidance and with radiographic contrast documenting appropriate placement in order to improve safety, accuracy, and potential efficacy of ESIs."([230])

Fredman et al published a paper in February of 1999([231]) in which they concluded that in cases of "failed back surgery syndrome" (for which ESIs are often used) "surface anatomy is unreliable and may result in inaccurate steroid placement. Finally, despite accurate placement, the depot-steroid solution will spread to reach the level of pathology in only 26% of cases."

Renfrew et al, published their study in 1999([232]), and concluded, "fluoroscopy is essential for correct placement of epidural steroid injection."

The International Spinal Injection Society (ISIS) has adopted the use of fluoroscopy. Firstly, in August 2000, Botwin et al ([233]) reported an incidence of 9.6% 'minor' complications per fluoroscopically guided transforaminal lumbar epidural injection. Amongst these were: 8 cases of increased back pain (2.4% of the total participants), 2 increased leg pain (0.6%). The authors did not report any major complications, but the follow up of only 1-3 weeks after each injection (a series being given over 4 months) would have failed to include such long-term effects as arachnoiditis.

Furman et al ([234]) published in *Spine* in October 2000 a study in which the authors contended, "there is a high incidence of intravascular injections in transforaminal ESIs that is significantly increased at S1."

They conclude, "Fluoroscopically guided procedures without contrast confirmation are instilling medications intravascularly and therefore not into the desired epidural location." As they point out, this requires that contrast injections should be performed in order to ensure correct placement of the steroid preparation.
More recently, Furman et al. ([235]) looked at the incidence of intravascular injection in cervical transforaminal injections. They found out of 504 transforaminal epidural steroid injections, the overall rate of fluoroscopically confirmed intravascular contrast injections was 19.4%. This was higher than for lumbosacral injections, confirming the need for fluoroscopic guidance. The authors also recommended use of contrast agent to exclude positioning intravascularly.

Stitz and Sommer ([236]) looked at the accuracy of blind versus fluoroscopically guided caudal epidural injections in 54 patients. Successful injection placement on the first attempt occurred in 74.1% of the patients, as confirmed by fluoroscopy. The authors remarked that whilst "Caudal epidural injection is performed ideally with fluoroscopic guidance as the gold standard for accurate drug placement," should fluoroscopy be impossible (contraindicated or not available), "the presence of readily palpable anatomic landmarks at the sacral hiatus and the absence of palpable subcutaneous airflow over the sacrum significantly increase the operator's confidence in the likelihood of an accurate injection". This was based on their observations that using these criteria, injections were confirmed on fluoroscopy as being 87.5% and 82.9% accurate respectively. However, that leaves over 10% inaccuracy, even allowing professional expertise at reading these signs.

Vad et al. ([237]) compared fluoroscopically guided transforaminal epidural steroid injections with saline trigger point injections in treating lumbosacral radiculopathy. Their prospective study required pain reduction greater than 50% at least 1 year after treatment to class as successful outcome. The group receiving transforaminal epidural steroid injections had a success rate of 84%, as compared with 48% for the group receiving trigger-point injections. This indicates the possible success for epidural steroid injections provided fluoroscopic guidance is used. However, as we have seen, practice varies widely.

EFFICACY:
Bernstein ([238]) looked at injection therapies in chronic pain and concluded: "There was limited evidence of effectiveness (level 3) of intraoperative steroid at discectomy, epidural steroid injection for sciatica with low back pain, caudal steroid injection for low back pain...There was limited evidence (level 3) that there is no additional benefit of adding steroid to local anesthetic in caudal epidural injections."

McQuay([239]) cites an NNT (number needed to treat one patient successfully) of 7.3 for greater than 75% pain relief in the short term(1-60 days) and 13 for more than 50% pain relief in the long term (12 weeks to 1 year). In comparison to adjuvant analgesics such as antidepressants and anticonvulsants, which have NNTs of between 2 and 3 for intractable neuropathic pain, ESIs are patently much less effective.
The recent Cochrane Review on Injection therapy for subacute and chronic benign low back pain concluded: "Convincing evidence is lacking on the effects of injection therapies for low back pain.**"**([240])

In New Zealand in 2002, a statement on the use of ESIs, prepared for distribution to members of the NZ Society of Anaesthetists stated:

"We suggest epidural steroids should be offered only in acute cases of disc herniation or nerve root ("radicular") irritation with either symptomatic criteria and/or with minor neurological signs... Equivocal cases or those with major neurological signs should be fully investigated, with MRI if necessary, prior to referral... It is our opinion, supported by the literature, that in carefully selected cases epidural steroid injection can produce rapid and sustained pain relief."

In December 2001, a Finnish group published a paper in the prestigious journal Spine ([241]), in which the authors suggested that with use of a methylprednisolone-bupivacaine combination, "In the case of contained herniations, the steroid injection produced significant treatment effects and short-term efficacy... For symptomatic lesions at L3-L4-L5... By 1 year, steroid seemed to have prevented operations for contained herniations"

However, they noted, "For extrusions, steroid seemed to increase the operation rate." They therefore concluded that steroids were "counterproductive" for extrusions.

This carries important implications in the cases where peridural injections are performed without the benefit of MRI diagnosis.

The diagnosis is critical: other sources of back and leg pain, including sacroiliac arthropathy, facet joint or myofascial pain are not likely to be relieved by this treatment. Patients who have had previous spinal surgery are unlikely to benefit, or those with long duration of symptoms, or spinal stenosis. Fukusaki et al. ([242]) evaluated the therapeutic effect of epidural steroids in lumbar degenerative spinal canal stenosis. They found that epidural block with saline (group 1) 8 ml of 1% mepivacaine (Group 2) or 8 ml of 1% mepivacaine and 40 mg of methylprednisolone (Group 3). Results showed that there was no significant difference in the effectiveness of treatment between group 2 and group 3 throughout the time course. In group 2, 55.5% showed a good or excellent result after 1 week, 16.7% after 1 month, and 5.6% after 3 months whereas in group 3, 63.2% after 1 week, 15.8% after 1 month, and 5.3% after 3 months. They concluded that epidural steroid injection was not beneficial in combating pseudoclaudication (stenosis symptom of leg pain on walking).

Rozenberg et al. ([243]) reviewed 13 trials from 1996-1997; 5 trials showed some benefit, 8 found no measurable benefits.

Rosen et al. ([244]) concluded in 1988, "overall results were poor", with only approximately 50% of patients receive temporary relief, whilst long-term relief occurs in less than 25% of patients. Anderson and Mosdal ([245]) found that epidural steroid injection was "useless" in patients with long-lasting complaints and previous disc operations.

This finding was also seen in the study by Cuckler et al. ([246]), which failed to demonstrate ESI efficacy, with the authors also raising the issue of published reports of "serious complications". More recently, in 1997, Carette et al. ([247]) studied patients with prolapsed nucleus pulposus and found that epidural steroid "offers

no significant functional benefit, nor does it reduce the need for surgery," although there may be short-term improvement in pain and sensory deficit.

Ringsdal et al. ([248]) proposed that "future correctly designed studies are necessary to clarify whether the injection should be a supplement to the established treatment of low back pain and sciatica," as they found that previous studies showed conflicting results.

The NHMRC report([249]) suggests that ESI are of greater use in sciatica when there is a substantial inflammatory component (especially if acute) but are less useful if there is a predominantly compressive radiculopathy .The AHCPR Clinical Practice Guideline ([250])clearly states that "Epidural injections are invasive and pose rare but serious potential risks. There was no evidence that epidural steroids are effective in treating acute radiculopathy."

Lafuma et al ([251]) conducted a randomised multicentre study to evaluate the benefits and costs of routine epidural steroid injections, using the primary criterion of whether other treatments were required following 1 to 3 injections: they concluded "adding an epidural injection as a first-line treatment...for the treatment of lumbosciatic syndrome requiring inhospital management results in additional costs and no gain in efficacy."

Again, this viewpoint was echoed by Schneeberger, et al in 1998([252]), who commented thus "To the present time no conclusive data have been published to prove that these procedures reduced the need for surgery in the case of herniated nucleus pulposus or spinal stenosis. Their efficacy on the intensity of pain is also controversial. Some improvement on pain and functional scores may be observed for a few weeks but this positive effect disappears 2 or 3 months post-injection."

The NZHTA Report in 2001 concluded: “Because of the lack of definitive evidence (either way), or the lack of well designed trials, a solid foundation for the effectiveness of steroids is lacking.”

Adverse reactions

These were clearly outlined by Kaplan and Derby ([253]):

"Risks associated with needle placement or with the injection of diagnostic/therapeutic substances, including the local anesthetic and steroid suspension, include infection, bleeding, nerve injury, transient numbness or weakness, paralysis, contrast reaction (allergy), adrenal suppression, and fluid retention with systemic manifestations which may include peripheral swelling. Pneumothorax may occur if undergoing a thoracic procedure. Total spinal blockade is possible with cervical procedures. There is also a potential for minor subcutaneous infection, vasovagal episode, as well as failure to obtain a definitive diagnosis or positive therapeutic injection with persistence of chronic pain."

Since the withdrawal of oil-based myelography, Depo-Medrone (Depo-Medrol) is one of the principal causes of adhesive arachnoiditis in the Western world. Dr. Burton maintains that almost all diffuse cases of clinically significant adhesive arachnoiditis are caused by Depo-Medrone.

However, the scale of the problem has yet to be recognised within the medical profession. The State of Colorado Invasive Treatment Procedures 1998([254]) states that "permanent paresis (weakness), anaphylaxis (acute allergic reaction of a life-threatening degree) and arachnoiditis have rarely been reported with the use of epidural steroids."

McLain et al. ([255]) noted that although epidural steroids are "commonly applied", this type of therapy "is not inherently benign". They reported a case of acute paraplegia resulting after an epidural injection carried out under fluoroscopic control, which was complicated by dural puncture. Radiographic studies showed a focal space-occupying lesion that spontaneously resolved within 2-3 hours. The patient recovered motor, sensory and bladder function over 48 hours. There were 3 possible explanations: 1. Inadvertent atypical anaesthetic block, 2. Loculation of the injectate caused a transient compressive lesion, 3. Intrathecal injection may have produced an arachnoid cyst.

Although in itself beneficial, the drug is in a solution that contains preservatives such as polyethylene glycol (also used in antifreeze). Nelson ([256]) states: "Methylprednisolone acetate contains approximately 30 mg of polyethylene glycol per milliliter"

Other preparations such as Kenalog use benzyl alcohol. It should be noted that alcohol is a recognised cause of toxic neuropathy, so adverse reactions are unsurprising.

The manufacturers, Upjohn, stated in 1981, **"We would advise against the epidural/extradural routes of administration because of possible adverse reactions**". However, this specific recommendation was withdrawn from the data sheet in 1997.

Upjohn included the following information in their 1988 data sheet:

"Adverse effects reported with some non-recommended routes of administration...

Intrathecal/epidural: arachnoiditis, meningitis, paraparesis/paraplegia, sensory disturbances, bowel and bladder dysfunction, headaches, seizures."

Currently, literature on Depo-Medrone states that it is **contraindicated for intrathecal administration** and that it contains benzyl alcohol, which is potentially toxic when administered locally to neural tissue. However, Bristol Myers Squibb, manufacturers of Kenalog, another steroid drug used in epidural injections, issues a data sheet stating, **"Not recommended for administration via the epidural route"**.

Both drugs remain unlicensed for use around the spine, the use being left to the individual doctor's discretion and clinical judgement. Their use in the UK is extensive and epidural steroid injection (ESI) is practised by a variety of clinicians including GPs and specially trained physiotherapists.

In 1993, David Blunkett raised the issue of Depo-Medrone in Parliament, but the Government's response was "The Department has issued no specific advice to doctors on this issue."

Later, in February of 1994, David Blunkett issued a news release calling for the halt of "all unrecommended use of this drug (depo-medrone)".

The Clinical Affairs Committee of the British Society of Rheumatology issued a statement to its members (1994) on epidural injection of Depo-medrone, which advises that because of the risks attached; if a doctor wishes to use it INDIVIDUAL INFORMED CONSENT would have to be obtained, "IN VIEW OF THE POTENTIAL SERIOUS COMPLICATIONS." They also recommended avoiding use of Depo-Medrol, suggesting other preparations.

Unfortunately this is not being adhered to. Department of Health statistics for 1995 suggest that approximately 30,000 epidural injections were performed that year in the UK. The numbers in the United States are likely to be considerably higher. The most commonly used preparation in the UK is Depo-Medrone.

In 1995, a letter in the British Medical Journal with the title, "A shot in the back" ([257]), responded to a World in Action programme that investigated claims that the drug manufacturer had pressurised doctors into giving the drug by an unauthorised route. The author concluded: "I had a clear impression that this was a specialised procedure to be used by experts and only by experts, entirely on their own responsibility. The drug company, in my view, had been wise not to press for an extension of the approval to include the epidural route. They have no control over the point of an anaesthetist's needle."

Nelson ([258]) cites a 2.5% risk of inadvertent injection directly into the subarachnoid space.
The Mackinnon studies on rats ([259]) showed that a variety of injectable steroids may damage peripheral nerves if injected directly into the nerve. Furthermore, the NHMRC report from 1994 suggested that the risk of dural puncture is, on average, "at least 5%". The authors also warn, "Particular care must be taken if attempting an epidural injection in patients previously treated by spinal surgery. Complete obliteration of the epidural space occurs following decompressive laminectomy and in such cases an attempted epidural injection carries a very high risk of dural tap."

Nelson maintains that "the epidural space is not wholly separate from the subdural and/or subarachnoid space" and that the spaces are "not only contiguous, but continuous". He therefore concludes that epidural delivery of drugs may not guarantee that the substance will remain isolated in the epidural space.

Byrod and Olmarker ([260]) found evidence that the potential barrier properties of the dura/arachnoid "seem less than effective" for preventing substances in the epidural space from reaching the endoneural space of nerve roots. Wood ([261]) studied the effects of injections of methylprednisolone acetate into rat sciatic nerves. Nerves treated with either the steroid or its vehicle showed damage, including collagen (scar) formation and demyelination.

Note that Crowhurst (in the context of epidural anaesthesia) maintains: "A drug placed in the epidural space will be re-distributed into various other compartments...fat, connective tissues, blood, epineurium sheaths, nerve roots and the spinal CSF. Only a fraction of the drug reaches the thecal nerve roots, its intended target. .....Unfortunately, the remainder of the dose is not without its unwanted effects..." ([262])

Recently, Nelson and Landau ([263]) again raised in the medical arena, the issue of the safety of ESIs, although their recent letter in the New England Journal of Medicine dealt with the use of intrathecal methylprednisolone to treat postherpetic neuralgia, as studied by Kotani et al. ([264]) Nelson and Landau noted that chemical meningitis accounts for half the serious sequelae of a single intrathecal injection of methylprednisolone. (40-80mg) Amongst the other adverse events, they cited cauda equina syndrome and chronic arachnoiditis, although they did concede that the latter was more often associated with multiple injections. They very pertinently mention the neurotoxic preservatives in the steroid preparation.

This is taken up by the Editor of the Journal, Dr. Watson ([265]) who, in his Editorial reply clearly states that the manufacturers, Pharmacia-Upjohn do not recommend their products either for intrathecal or **epidural** administration. Whilst they concede that it is possible to manufacture a preservative-free preparation, they feel a delay before marketing is a substantial barrier i.e. it is not commercially advantageous to develop such a preparation.

A German practitioner, Dr. Henner Niebergall, of Freiberg, has questioned the use of a combination of methylprednisolone and lidocaine ([266]). He pointed out that: "lidocaine is neurotoxic not only when injected into the nerves but also when injected intrathecally at concentrations greater than 2 percent." Note that in most cases, epidural steroid injections involve a combination of local anaesthetic for immediate effect and steroid preparation for sustained anti-inflammatory action.

In reply, Kotani et al, the authors of the original study, remarked that they were fully aware that "intrathecal methylprednisolone can be neurotoxic" (232). They excluded patients with neurologic disease from the study, based on the observations that complications had been seen in multiple sclerosis patients. They admitted that their consent form clearly stated in detail about "the possibility of serious adverse effects, including life-long paralysis, exacerbation of pain, recurrence of herpes zoster, and even death."

More recently still, Marinangeli et al. in July 2002, published a paper ([267]) on the clinical use of epidural and spinal steroids. The authors noted: "Complications associated with intrathecal steroids are more frequent and severe than epidural injections and include: adhesive arachnoiditis, aseptic meningitis, cauda equina syndrome. Steroidal toxicity seems to be related to the polyethylenic glycol vehicle."

Nelson and Landau published a detailed account of the history of the use of intraspinal steroid preparations ([268]) in 2001. Whilst they stated that serious permanent complications including arachnoiditis are "a rare but certain risk", they went on to stress that "We must conclude that the adverse drug reactions of

intraspinal steroid therapy submitted to the FDA (and especially individual case reports in the literature) comprise only the 'tip of the iceberg.'"

Other reports of complications:
Recently, Parsons and Hawboldt reported on herpes zoster as a complication ([269])
In 1997, Siegfried reported a case of CRPS (RSD) development after cervical epidural steroid injection. This condition has similarities with arachnoiditis (see below). ([270])
Jarrier et al. reported a case of Cauda Equina Syndrome. ([271])
Staphylococcal meningitis and cauda equina syndrome were reported in a Canadian patient after a series of epidural steroid injections. ([272])
Intrinsic cord damage as a result of 'pithing' the cervical cord with the needle has also been reported. ([273])
Chronic arachnoiditis after use of paramethasone, a steroid available outside the USA, was reported in 1997. ([274])
Enlargement of a chronic aseptic epidural abscess by epidural injections was reported by Sabel et al. ([275]) who suggested: "The frequent use of invasive procedures at the spinal cord such as epidural injections has led to an increased incidence of iatrogenic abscesses."

Temporary complications include retinal haemorrhage ([276]) Young ([277]) reported in 2002 on a case of transient blindness after lumbar epidural steroid injection. The author noted that there had been 9 previous cases of retinal haemorrhages such as in this case. Whilst the patient recovered most of his sight, he did not regain full sight. The author concluded: "Transient blindness is a rare complication of lumbar epidural injection."
Gibran et al. ([278]) reported a case of unilateral vitreous haemorrhage secondary to a caudal epidural injection, which they suggested was a variant of a condition known as Terson's syndrome.

Stoll and Sanchez ([279]) reported a case of epidural haematoma after spinal puncture for delivery of steroid, presenting 8 days after the procedure. This has more usually been reported in association with impaired haemostasis (not seen in this case) and epidural anaesthesia. Of note is the delay between procedure and clinical presentation, and the potential for later arachnoiditis due to the inflammatory properties of blood within the haematoma. .....
Other case reports of epidural haematoma include: ([280];[281]) Reitman and Watters ([282]) reported a fatality after a cervical epidural steroid injection. The patient developed an anterior subdural haematoma, which was surgically decompressed (and a patch applied), but she subsequently developed meningitis and succumbed to repeated cardiac arrests.

Conus medullaris syndrome was reported by Cohen in 1979, after multiple intrathecal steroid injections. ([283])

A further important point was raised by Lowell et al ([284]) when they reported on 3 cases of epidural abscess

after intrathecal methylprednisolone administered after discectomy. They concluded that the use of perioperative epidural steroid injections may predispose to infection and that a prospective study is needed to examine the use of this procedure: "Therapy was discontinued after an increased postoperative deep infection rate was noted."

There have been a number of case reports of epidural abscess. ([285];[286];[287], [288], [289])
O'Brien and Rawluk described an unusual case involving Mycobacterium organism. Histology of the excised inflammatory lesion showed chronic granulomatous inflammation. ([290])
Kaul et al. ([291]) reported an extradural abscess in a 26 year old presenting as an external swelling.

Horlocker et al. ([292]) looked at patients taking non-steroidal inflammatory drugs (NSAIDs) who underwent ESIs, to evaluate any increased risk of haemorrhagic complications such as spinal haematoma. In their series, only 28% of cases involved fluoroscopic guidance; paraesthesia was elicited in 3% and dural puncture occurred in 0.8%. The mean volume of injectant was 8 +/- 3 mL. 61% included local anaesthetic agent (52% lidocaine, 9% bupivacaine). The steroid used in 98% was triamcinolone.
Blood was noticed during needle or catheter placement in 5.2% of the patients (including frank blood in 12 patients), but NSAID therapy did not appear to affect the incidence of traumatic (bloody) tap. The authors noted, however, that there was an increased frequency of minor haemorrhagic complications with increasing age, large gauge needles, needle placement at multiple interspaces, multiple needle passes, larger injectant volume and accidental dural puncture. 42 out of 1035 patients experienced new neurological symptoms or worsening of previous complaints; 18 had bilateral symptoms. This was more common in women than men. It is unclear as to the extent of follow-up in these cases.
The authors noted in their discussion that new antiplatelet drugs such as ticlopidine and clopidogrel have been associated with cases of spinal haematoma including one patient undergoing a series of epidural steroid injections. Vandermeulen et al. ([293]) attributed 3 of 61 cases of spinal haematoma after spinal or epidural injections, to antiplatelet medication. However, other studies have claimed that spinal injection given to patients taking aspirin or other NSAIDs is relatively safe. Indeed, the American Society of Regional Anesthesia Consensus Conference on Neuraxial Anesthesia and Anticoagulation concluded: "antiplatelet drugs, by themselves, appear to represent no added significant risk for the development of spinal hematoma in patients having epidural or spinal anesthesia."
In commenting on the 42 patients with transient worsening of neurological function, Horlocker and her colleagues initially attributed this to the local anaesthetic in the injectant, but decided that the duration of symptoms over a number of days and the fact that patients not receiving LA, militated against this. They speculated on a pressure (ischaemic) effect of the injection or an inflammatory response. Either scenario could be a precursor to arachnoiditis.

Chemical meningitis

Gutknecht ([294]) described chemical meningitis after epidural steroid injections.

Karmochkine et al. ([295]) described a case simulating infectious meningitis after intradural steroid injection.

Dougherty and Fraser ([296]) also reported 2 cases of severe meningitis following intraspinal steroid administration. The authors concluded: "It is suggested that the value of intraspinal steroids in the treatment of disc-related sciatica is unproven and if they are used, one must be alert to the complications."

THE TIRANTI CASE On February 3, 2000, a 38 year-old woman in New Jersey, USA was awarded $12 million as compensation for arachnoiditis which developed as a result of Depo-medrol injected into the subarachnoid space in 1986. The size of the award was in compensation for her past and future disability as well as her pain and suffering.

Conclusion:

In summary, in 1985 Kepes and Duncalf ([297]) wrote:

"Low back pain and sciatica have been treated with peridural local anesthetics for over 80 years and with epidural and subarachnoid steroid injections for a quarter of a century. Good results from this treatment, which vary from 20 to 95% decrease on long-term follow up. Statistical significance is absent if compared with other forms of therapy. It is the authors' opinion that the rationale for the use of spinal local analgesics or steroids or intramuscular steroids has not been scientifically proven. Complications with the use of subarachnoid steroids are sufficiently serious that this form of therapy should be condemned. In this age of accountability it is imperative that therapies with questionable benefits should be critically evaluated."

Nearly 15 years later, Dr. Burton, one of the leading experts on arachnoiditis, wrote in 1999, ([298])
"A universally popular treatment is the percutaneous deposition of steroids into the epidural space of the spinal canal in order to decrease inflammation and assist with the natural healing processes. Unfortunately, because of physician failure to know about, or to understand, the potentially dangerous potential of certain steroid substances known to be able of creating disabling adhesive arachnoiditis this disease process still remains rampant throughout the world. "

Quantifying the overall risk of developing symptomatic adhesive arachnoiditis solely as a result of epidural steroid administration is fraught with difficulties because most cases involve a variety of other invasive procedures and also there is unlikely to be direct MRI evidence to permit a comparison of pre- and post-epidural scans. However, in broad terms, bearing in mind Nelson's suggestion of 90% incidence of radiological arachnoiditis following *intrathecal methylprednisolone,* and the NHMRC estimate of 5% dural puncture, one can estimate an approximate rate of radiological arachnoiditis of 5% after epidural steroids. Add in results from Johnson et al.([299]) who found that 20% of those with radiological arachnoiditis subsequently developed symptoms, and one can suggest an overall estimate of 1% for the risk of symptomatic adhesive arachnoiditis following epidural steroid injection. This is far higher than the figure suggested by most published medical literature, which may be accounted for by the confounding presence of other precipitating factors, and also the overall low rate of detection of the condition.

"The complications of ill-advised epidural steroid injection represent one of the most serious and under appreciated public health problems in the world today. Because many have not learned from the past adhesive arachnoiditis continues to be caused in unsuspecting patients by physicians who don't do the "right thing" because they don't know what it is."([300])

Epidural anaesthetics are another group of drugs implicated in causing arachnoiditis. Vandermeulen ([301]) includes arachnoiditis as a "mishap"... "solely due to ... epidural anaesthesia". Haisa et al ([302]) state that lumbar adhesive arachnoiditis should be considered for differential diagnosis of back pain and leg pain after epidural anaesthesia. Furthermore, epidural anaesthesia may cause subarachnoid cysts or cavities, which are also recognised complications of arachnoiditis.

Over a century ago, Koller first used cocaine to anaesthetise his eyes. In 1865, Halsted used cocaine anaesthesia. Corning pioneered the epidural local anaesthetic block, whilst Bier reported on subarachnoid local anaesthetic in 1899. (Bier also reported the first spinal headache). Lemmon in 1940 started using a continuous spinal technique; later intraoperative spinal anesthesia came into use; however, it was not until the 1990s that infusions of post-operative analgesia became widespread. ([303])

Epidural and spinal administration of anaesthetic agents is used for:

- Childbirth
- Post-operative pain relief
- Regional anaesthesia : e.g. for knee operations

Aldrete, an anaesthetist with considerable experience with arachnoiditis patients, has recently written a paper about arachnoiditis following regional anaesthesia. ([304])

He begins by stating:

"Of late, regional anaesthesia has enjoyed unprecedented popularity; this increase in cases has brought a higher frequency of instances of neurological deficit and arachnoiditis."

He notes that in the early stages this may manifest as transient radicular irritation, cauda equina syndrome and conus medullaris syndrome, whereas later, it cause radiculitis, nerve root clumping, scarring, dural sac deformities, pachymeningitis, pseudomeningocele, and syringomyelia.

With regard to regional anaesthesia in particular, arachnoiditis arises as a result of traumatic puncture (blood, damage to neural structures), the toxicity of the anaesthetic agents themselves, detergents/antiseptics, and epidural abscesses or meningitis.

Aldrete points out that the old adage 'all anaesthetics are neurotoxic' and Pizzolatto's prediction of this, seem to be proved correct by experience. Even lower concentrations of anaesthetic agent such as 2% lidocaine, have been reported as neurotoxic. ([305])

High dose, high concentration and prolonged exposure are all risk factors in neurotoxicity. Weighting with dextrose (to provide hyperbaric solutions) or use of vasoconstrictors such as epinephrine, are further causes for concern.

Burm([306]) states that epidural anaesthesia results from the interactions of local anaesthetics with nerves within the subarachnoid space, which they reach by uptake into the epidural fat and via systemic absorption, and that consequently, epidural doses need to be much higher than spinal doses. Bearing this in mind, it is unsurprising that there is evidence that epidural anaesthetic agents such as those used in childbirth also carry a risk of neurological damage.

In 1996, Gallo et al, in Italy, ([307]) compared the use of 1% and 0.5% hyperbaric bupivicaine administered intrathecally for Caesarean section. The authors reported little difference in the efficacy of the two concentrations and remarked: "In view of the possible relationship between the neurotoxicity of local anaesthetics and the concentration of the solution used for spinal anaesthesia, it is to be hoped that less concentrated solutions of hyperbaric bupivicaine will be introduced."

As Malinovsky and Pinaud noted (also in 1996[308]), neurotoxicity of anaesthetic agents can be due to:

- Reduced neuronal blood supply
- High concentrations
- Long duration of exposure
- The use of adjuvants.

They reported Cauda Equina Syndrome following continuous spinal anaesthesia using hyperbaric lidocaine and tetracaine. The authors clearly recommended the use of preservative-free solutions.

Meanwhile, Ganem et al ([309]) had studied the neurotoxicity of subarachnoid hyperbaric bupivicaine in dogs. They found that "Increasing doses of hyperbaric bupivicaine solutions increased the incidence of nerve tissue damage, which did not occur using hypobaric solutions."

A study published in the British Journal of Anaesthesia in 1995([310]) by Tarkkila et al found that with 5% lidocaine, there was a 10% incidence of transient radicular irritation, which was not however seen with bupivicaine.

Ginther and Zamanian, in an Internet publication, "Toxicity, Local Anaesthetics from Emergency Medicine/toxicology" ([311]) noted:

"Very high doses of anesthetics can produce irreversible conduction block in less than 5 minutes. Peripheral neurotoxicity, such as prolonged sensory and motor deficits, has been documented. It is hypothesized that a combination of low pH and sodium bisulphite in the mixture can be partially responsible for these changes."

Lidocaine and tetracaine appear to have a greater potential for neurotoxicity than bupivacaine at clinically relevant concentrations. Hodgson et al. ([312]) listed a number of different studies in which spinal

anaesthesia caused transient neurological symptoms (TNS). In particular, it is worth noting the findings of Hampl ([313]), with gynaecology patients; 31% experiencing TNS after 5% lidocaine, 40% after 2% lidocaine and in a separate study ([314]), 33% with 5% lidocaine plus 7.5 glucose, and 31% with 5% lidocaine plus 2.7 glucose (cf. 0% with 0.5 % bupivicaine which is now in wider use).

Yamashita et al. ([315]) recently published the results of a rabbit study looking at the comparison of neurotoxic effects on the spinal cord of 2% tetracaine, 10% lidocaine, 2% bupivicaine and 2% ropivicaine administered intrathecally. They found "sensory and motor functions in the lidocaine group were significantly worse than in the other groups," significantly raised glutamate concentrations and characteristic histopathological changes: vacuolisation of the dorsal funiculus and chromatolytic damage of motor neurons. They concluded: "The margin of safety may be smallest with lidocaine."

Horlocker wrote in 2001([316]) about neurological complications of neuraxial blockade. She noted that incidence of transient neurologic symptoms (TNS), first described in 1993, has ranged between 0 and 37%, "and is dependent on anesthetic, surgical and, possibly, undefined patient factors." Freedman et al. ([317]) in a large study, found incidence of TNS with lidocaine (11.9%) was significantly higher than that with tetracaine (1.6%) or bupivacaine (1.3%). Pain was described as severe in 30% of patients and resolved within a week in over 90% of cases. Obesity and lithotomy position were noted as particular risk factors. Horlocker noted: "The clinical significance of TNS is unknown. While many anesthesiologists believe that the reversible radicular pain is on one side of a continuum leading to irreversible cauda equina syndrome, there are currently no data to support this concept." She also remarked "The blood supply to the spinal cord is precarious due to the relatively large distances between the radicular vessels. Systemic hypotension or localized vascular insufficiency with or without a spinal anesthetic may produce spinal cord ischemia resulting in flaccid paralysis of the lower extremities, or anterior spinal artery syndrome."

Birnbach ([318]) writing on Controversies in Obstetric Anesthesia devoted the last section of his article to the question: "Should we still be using 5% spinal hyperbaric lidocaine?" He argues that one of the reasons we are seeing "an increased incidence of lidocaine-related neurologic sequelae" is that these problems always existed but are only now being looked for and thus recognised. He notes a "heightened awareness" of this problem due to the literature on cauda equina syndrome caused by lidocaine and microcatheters.

ASTRA USA, acknowledging reports of transient radicular symptoms, has advised all US anesthesiologists to use caution with hyperbaric spinal lidocaine 5%, as follows:

1. Dilute 5% lidocaine with equal volumes of CSF or preservative free saline
2. Limit the dose to a maximum of 100mg
3. Remove and replace the needle if an additional dose is necessary
4. Use a needle of sufficient gauge to allow adequate withdrawal of CSF before and after spinal administration.

If the epidural space is already compromised by disc herniation, stenosis or epidural fibrosis, the risk is greater. Yuen et al ([319]) state that neurological complications "may be more severe in the presence of spinal

stenosis". The presence of a preexisting neurologic condition may predispose the nerve to the neurotoxic effects of local anaesthetics. ([320])

Rocco et al ([321]), in a study of pressure gradients in the epidural space, concluded that as resistance to inflow of fluid was significantly higher in the diseased epidural space, "spread of anesthetics might be difficult to predict".

Whilst a British paper published in February 2001 ([322]) refuted the impact of epidural anaesthesia on long-term backache for up to a year post-procedure, there are questions that remain to be answered as to the risk of long-term neurological sequelae, which seem not to have been addressed as yet (studies to date concentrating on back pain but not necessarily on neurological problems).

The Patient Injury Act in Finland in 1987 initiated a scheme where patients can claim damages on a no-fault compensation basis via the Patient Insurance Association (PIA). Aromaa et al. ([323]) looked at severe complications associated with epidural and spinal anaesthesias between 1987 and 1993 in Finland, based on insurance claims. Out of 86 claims, 25 involved serious complications of spinal anaesthesia. These included one case of permanent cauda equina syndrome, 7 of neurological deficits and 4 infections. 9 cases of serious complications of epidural anaesthesia were reported, including paraparesis (1), permanent cauda equina syndrome (1), peroneal nerve paresis (1), neurological deficit (1), bacterial infections (2), acute toxic reactions related to the anaesthetic solution (2), and overdose of epidural opioid (1).

Using these results, the authors proposed incidence figures of serious complications: 0.45:10,000 following spinal and 0.52:10,000 following epidural anaesthesia.

Swedish authors Moen, Irestedt and Raf ([324]) reviewed claims from Patient insurance between 1997 and 1999, noting that "These occurred more frequently after epidural anaesthesia (1:4,000) than after spinal anaesthesia (1:13,000) with the exclusion of obstetric epidural anaesthesia (1:40,000)". Epidural haematoma occurred in 1:30,000 after epidural anaesthesia, in 1:200,000 after spinal anaesthesia. One epidural abscess occurred in 60,000 epidural anaesthesias, while five cases of meningitis occurred after spinal anaesthesia (1:40,000). Out of 65 claims, 29 involved serious neurological complications.

Chiapparini et al. ([325]) looked at the outcome of severe complications of lumbar epidural anaesthesia in 16 patients. 4 had symptoms immediately after the procedure. 1 developed subacute flaccid paraparesis. 2 others had infectious spondylodiscitis at lumbar puncture level.

8 patients had a delayed progressive spastic paraparesis, which was found to be due to "subarachnoid cysts and irregularities of the surface of the spinal cord consistent with arachnoiditis"; of these, 6 had an "extensive, complex syrinx within the cord". 1 patient had a severe lumbar polyradiculopathy, as a result of cauda equina adhesive arachnoiditis revealed on MRI. The authors noted what they termed a "relentless progression of the disease and a poor outcome" for the patients with arachnoiditis; 5 were wheelchair bound, one bedridden.

They remarked: "Although epidural anaesthesia is generally considered safe, rare but severe complications, such as radiculopathy, infectious disease, myelopathy from ischemia and arachnoiditis with a syrinx may occur."

In conclusion, the Italian authors stated: "Complications of epidural anaesthesia are easily recognised when they develop immediately; their relationship to the anaesthesia may be ignored or underestimated when they appear after a delay. Awareness of the possibility of delayed complications is important."

The problem with many cases of arachnoiditis is that there can be a considerable delay between the triggering procedure and onset of the symptoms.

One of the causes for these complications might be skin particles: Reina Perticone et al. ([326]) discussed the drawing of epithelial (skin) cells into the vertebral canal during spinal injections. They mentioned early complications such as meningitis and later ones such as epidermoid tumour. Using cats, they conducted postmorterm analysis of meninges after subarachnoid anaesthesia using 0.7-1ml bupivacaine 0.5%. Whilst no epidermal cells were found on the meninges' surface, an epithelial cell was observed inside a sectioned epidural vessel towards the systemic circulation. The authors suggested that subarachnoid anaesthesia using a 22G Quincke needle might allow skin fragments to enter the spinal canal.

In patients who have experienced paraesthesia during administration of epidural anaesthesia, there is a risk of neurological complications. Aldrete remarked (267):
"Direct trauma to nerve roots or the spinal cord may be manifested as paraesthesia that has not been considered an injurious event; however, it usually implies dural penetration, as there are no nerve roots in the epidural space posterior."..."It has been realized that paraesthesia provoked in peripheral nerve trunks not only implies nerve contact but frequently represents a puncture."
Selander ([327]) reported a 2.8% incidence of neurological complications in patients in whom painful par aesthesia was deliberately induced. If the perineurium integrity is compromised, herniation, loculation and scarring of the intraneural structures may result.
In addition, one must consider the effects of a neurotoxic substance on a damaged and therefore susceptible, nerve: Aldrete commented: "Furthermore, the persistent pursuit of the anesthetic technique by injecting the local anaesthetic upon and around a nerve root with a perforated myelin sheath may turn an otherwise usually innocuous concentration of LA into a neurotoxic agent."
Indeed, he recommended:
"Reassessment of the impact of paraesthesia as generator of a potential neurological deficit when LA is injected into or around it, includes the consideration to immediately discontinue the procedure rather than attempt another puncture at a different intervertebral space, as a hole in the dura has already been made."

Aldrete also mentioned an important point: the increasing trend for performing regional anaesthesia on patients who are unconscious, having already been given a general anaesthetic. He cited Bromage and Benumof ([328]) who reported on paraplegia following accidental intracord injections. He noted that many paediatric anaesthetists practice regional and general anaesthesia together in infants and children.

Pleym and Spigset ([329]) surveyed 21 cases of peripheral neurological deficit related to subarachnoid or epidural anaesthetic. The patients experienced:
Pain in the lower extremities reported in 12 (57%), paraesthesias/hypoaesthesias reported in 11 patients (52%), low back pain or abdominal pain from T9-T10 downwards in 7 (33%), urinary incontinence in 3 patients, faecal incontinence in 2 patients, and erectile dysfunction, loss of sensation of full bladder and quadriceps muscle paresis were each reported in one patient. There was a group with reversible symptoms and another group who had persistent symptoms after 1 month to 4 years. 50% of the latter group had motor deficits.
Although the authors concluded: "causal relationship between subarachnoid or epidural administration of local anesthetics and neurologic deficits therefore remains uncertain," they also pointed out the increase in the number of reports on lidocaine after the introduction of very fine-bore spinal needles, which they noted as being "consistent with the suspicion that lidocaine at the concentration 50 mg/ml is neurotoxic and that it may not be diluted rapidly enough in the cerebrospinal fluid when injected through these needles".

Mateo et al. ([330]) reported on a rare complication: pneumocephalus. They had 2 cases, after "loss of resistance" technique (using an air-filled syringe) was used for epidural injection; one was an epidural collection of air, the other subarachnoid.
Previously, Saberski et al. ([331]) reviewed the complications related to the use of air in determining the loss of resistance in order to identify the epidural space for injections. There were few studies comparing saline with air during the review period (1966 to 1995) but a number of case reports. The authors noted: "Complications associated with the use of air for the loss of resistance technique included pneumocephalus, spinal cord and nerve root compression, retroperitoneal air, subcutaneous emphysema, and venous air embolism. Additionally, inadequate analgesia and paresthesia have been associated with the loss of resistance technique using air. Transient and permanent neurologic sequelae have been attributed to some of the complications."
They concluded: "The potential complications associated with the use of air for identifying the epidural space with the loss of resistance technique may outweigh the benefits. The use of saline to identify the epidural space may help to reduce the incidence of these complications."

Vartis, Collier and Gatt ([332]) in Australia, discussed the potential intrathecal leakage of drugs injected as a bolus via and epidural catheter during combined spinal anaesthesia (CSE). CSE involves a deliberate multicompartment block across a breached dural membrane. Whilst in their study, they did not observe evidence of this leakage, the authors counselled caution during administration of a bolus dose of drug, especially hydrophilic opioids.

Di Tommaso et al. ([333]) recently reported: "Severe complications such as spinal epidural haematoma and an array of adverse neurological events leading to temporary or permanent disability have been ascribed to central neuraxial blocks. Infections (meningitis, abscesses), chemical injuries and very rarely cerebral ischaemia or haemorrhage, or both, have also been ascribed directly or indirectly to spinal and/or epidural anaesthesia. Some case reports, and very few retrospective

studies, have focused their attention on the fact that central nerve blocks can cause, albeit rarely, permanent damage to the spinal cord or nerve roots, or both."

Butamben is a local anaesthetic that provides extended sensory blockade, which has led to the use of 5% butamben administered epidurally in cancer patients to relieve pain uncontrolled by systemic opioids. ([334]) However, once again, we need to consider possible adverse effects. (Many drugs used in chronic non-malignant pain were originally developed for patients with terminal illness where longer-term effects were less relevant). Shulman, Joseph and Haller ([335]) looked at the effect of 10% butamben on dogs. They found that if it was injected intrathecally (a single injection), the dogs developed arachnoiditis, whereas epidurally (given 3 times) appeared to be safe. The authors also reported on 2 cancer patients who at autopsy were not found to have significant pathology in the spinal cord, meninges or spinal nerves. They concluded: "Epidural butamben does not appear to cause any local tissue damage provided that subarachnoid needle placement has been ruled out. Subarachnoid butamben should be avoided."

Conclusion: The Cochrane review in February 2000 ([336]) commented, "Epidural analgesia appears to be very effective in reducing pain during labour, although there appear to be some potentially adverse effects. Further research is needed to investigate adverse effects and to evaluate the different techniques used in epidural analgesia."

Epidural blood patch:

Unintentional dural puncture during attempted epidural anesthesia occurs with a reported incidence of 1-5% depending on operator experience. Because of the large size of epidural needles, post dural puncture headache (PDPH) following dural puncture occurs in as many as 85% of patients.

Treatment for this headache is often a 'blood patch' where blood is taken from the patient's arm and injected into the epidural space to plug the hole in the dura. Typically 15 to 20 ml of blood is injected into the epidural space at the level of the dural puncture. As much volume as possible is injected until the patient begins to complain of back or leg discomfort. Although immediate relief occurs in up to 90% of patients, headache returns in over half, so that a second injection or a continuous infusion may be necessary to produce sustained relief.

Unfortunately, this treatment is not without risk and can have unwanted effects. Use of prophylactic epidural blood patches is controversial. Common side effects of epidural blood patch include pain at the site of injection and back and lower extremity discomfort. Less common complications include compression of nerve roots and radiculopathy with resultant with lower extremity sensory disturbances and weakness. Blood in the subarachnoid space is highly irritant and can cause arachnoiditis. If performed within the first 24 hours, an EBP is ineffective in 70% of cases (4% in patients after 24 hours). ([337]) Duffy and Crosby ([338]) reviewed the technique of EBP and found that it fails to provide symptomatic relief in 25-30% of PDPH. Other possible treatments for post-dural puncture headache include caffeine and non-blood products such as saline instead of blood.

Whilst epidural crystalloid preparations appear less effective than blood, an isolated report suggested that Dextran 40 might be useful; the authors of the review, however, express concern as to safety

considerations.

Although prophylactic measures are being investigated, EBP will no doubt continue to be used in patients who suffer inadvertent dural puncture in a variety of epidural procedures. This of course, contributes further to the risk of arachnoiditis associated with perispinal injections.

Lithotomy position

Gordh (from the Karolinska Hospital in Stockholm) has suggested that back pain is due to the muscle relaxation caused by the spinal anaesthesia, especially under stretched conditions, such as on the operating table. ([339])

Spinal anaesthesia with lidocaine results in a profound motor block in anaesthetised segments ([340]), which can lead to a supramaximal flattening of the lordotic arch causing extreme hyperextension of ligaments and muscles. This in turn may impair blood circulation in muscles, leading to accumulation of lactic acid, and might possibly cause tiny, microscopic ruptures in the myofascial tissues, perhaps with miniature haemorrhages. These changes may later induce inflammatory reactions in the lumbosacral area which, whilst relatively focal, are nevertheless painful.

Flattening of the lumbar lordosis will be more pronounced in the lithotomy position, as described by Schneider et al. ([341])

The pain would typically be symmetric in the lumbosacral area and radiate into the buttocks and possibly thighs, and tends to respond well to ordinary analgesics and NSAIDS.

However, if this was a purely myofascial stress syndrome, one would expect the inflammatory reaction to subside within a few days, and the pain to resolve. It may well be that the lumbosacral nerve roots are affected by the combination of the lithotomy position and the spinal anaesthetic.

The lithotomy position may also contribute to pooling of the anaesthetic agent in the cauda equina, which increases the risk of neurotoxicity.

Gumus et al ([342]) found that of 1170 patients operated on in the lithotomy position, 1% developed post-operative neuropraxic complications. Of the 12 patients affected, 2 developed permanent deficit.

Epidural catheters:

Sarubbi and Vasquez ([343]) described spinal epidural abscess due to temporary epidural catheters. They reported 2 cases and discussed a further 20 from medical literature. On average the patients had the catheter indwelling for 3 days, and developed symptoms within 5 days. 63.6% had major neurological deficits, and 22.7% also had concomitant meningitis. Staphylococcus aureus was the predominant pathogen. 38% of the patients had persistent neurological deficit.

Infections can also, of course, arise in permanent catheters. Madaras-Kelly et al. ([344]) described an unusual case of mycobacterium meningitis associated with a contaminated indwelling epidural catheter.

Smitt et al., in The Netherlands, ([345]) looked at the use of indwelling epidural catheters to treat cancer pain.

They found that of 91 patients, technical complications and superficial infections occurred in as many as 43%, whilst deep infections occurred in 12 patients, 11 of whom had a spinal epidural abscess. They concluded: "Deep infection is a frequent complication of epidural analgesia and is associated with a high morbidity and mortality. Only cancer patients with a short life expectancy (< or =3 months) should be treated with epidural analgesia."

Meningitis:

1. Bacterial:

French authors Gorce et al. ([346]) reviewed meningitis as a complication of spinal/epidural anaesthesia. They noted that the sources of contamination are most often from the patient's skin flora or the anaesthetist's ear/nose/throat flora. They also mentioned aseptic meningitis arising from irritant substances in the subarachnoid space. Bacteria in the blood (bacteraemia) or spreading local infection were another source. The authors remarked that meningitis is "a severe and uncommon complication of both spinal and epidural anaesthesia."

Bouhemad et al., also in France, reported a case of Streptococcal meningitis following combined spinal-epidural anaesthesia for labour. ([347])

German authors Beland, Prien and Van Aken ([348]) discussed administration of epidural anaesthesia in patients with systemic infections (bacteraemia or septicaemia). They pointed out that usually this is regarded as an absolute contraindication for CNS block. They suggested that infection might spread due to accidental vessel puncture, a change of pressure in the subarachnoid space, or the induction of a "locus minoris resistentiae." Whilst in animals meningitis can be induced by subarachnoid puncture during bacteraemia, there has not been an equivalent study that proves an increased risk for bacteraemia human patients. The authors remark that transient bacteraemia is common, especially in urological and obstetrical-gynaecological procedures (which are often done using regional rather than general anaesthesia), but the incidence of infectious complications is actually quite low. Nevertheless, they advise: "Antibiotic chemoprophylaxis should be given before the puncture and the patients must be closely followed after the anaesthesia, particularly for the development of spinal epidural abscess. Because of the possibly increased risk of infectious complications, informed consent should be obtained from the patient."

Okano et al. ([349]) reported a case of spinal epidural abscess associated with epidural catheterisation, and reviewed a further 29 similar cases in the medical literature. 11 of the 30 patients had some underlying disorders, including malignancy or herpes zoster, or were receiving steroids. 9 of the 10 patients with thoracic epidural abscess had persistent neurological deficits, whereas 12 of the 15 patients with lumbar recovered fully after treatment. The authors noted that thoracic abscesses are associated with a poor prognosis.

Kranke et al. ([350]) reported a case of lumbar epidural Staphylococcal abscess after a catheter epidural anaesthesia in a fit 34 year old woman who underwent knee surgery. 7 days after operation, she experienced lumbar pain, headache and meninges. MR revealed an epidural abscess at L3-4, which was drained surgically.

EPIDURAL POST-OPERATIVE PAIN RELIEF

Increasingly this is common practice throughout the UK. It is particularly used in children and the elderly to enhance the level of pain relief. Patient Controlled Anaesthesia allows the patient to ensure that he/she remains comfortable. Anaesthetists may prescribe a PCA machine for several days or offer the option of an epidural block. In an epidural block, a needle is placed into the epidural space and a small catheter is then threaded through the needle into the space; the needle is then removed. Local anaesthetic solution or a combination of local anaesthetic mixed with a low dose of narcotics can then be injected through the catheter or a continuous infusion can be maintained for several days. In children, the epidural catheter tends to be introduced whilst the patient is still under general anaesthetic to avoid pain and distress; however, there are risks attached to this, particularly that the patient is unable to protest should the procedure cause inadvertent misplacement of the needle (damaging nerve roots for example).

A paper in 2000 ([351]) described 10 cases of infection associated with the use of epidural catheters for post-operative pain relief between 1997 and 1998. A case control study showed that the infections were commoner in the summer months and associated with analgesia infused by syringes rather than pumps.

SPINAL OPIATES:

In patients with chronic pain, whether cancer-related or non-malignant, may be offered intrathecal drug therapy ("the pump") or intraspinal narcotic analgesia (INA). There are significant risks with this form of therapy, including the risk of causing or exacerbating arachnoiditis.

Initially designed to give superior analgesia to the terminally ill, avoiding intolerable side effects, the 'pump' is now used for chronic non-malignant pain. This means that continued use over decades may be proposed and as yet we are unable to say for certain how safe that may be.

A study on the neurotoxicity of intrathecal agents ([352]) suggests that complications may occur in patients after high doses of morphine. These were related to one of its metabolites, morphine-3-glucuronide. High concentrations of intrathecal morphine produce an allodynia and hyper-reactivity that may be related to this metabolite (Yaksh et al, 1986; Yaksh and Harty, 1988).

Yaksh, ([353]) writing on the toxicology of intrathecal morphine, has noted, "Continuous intrathecal infusion of morphine is widely used in chronic pain management. In spite of, and perhaps because of its long history of use, there have been no systematic safety studies on the effects of continuously infused morphine sulfate. Now convergent preclinical and clinical observations suggest the consequences of this omission."

He also comments on the doses used. In general, patients may receive up to 20 mg/day with long pump refill intervals, so " it is likely that patients routinely receive morphine at concentrations which exceed even that which is commercially available (e.g. 25 mg/mL), employing concentrations of morphine which are at or near the absolute solubility of morphine sulfate (e.g. 50-55 mg/mL). Market research indicates that approximately 80% of morphine used in implanted pumps is compounded (*K Hildebrand, Medtronic Corp. personal communication)*."

In humans, the doses of morphine associated with granulomas frequently exceeded 20-25 mg/day. However, Yaksh suggests a combination of causative factors: reaction to catheter or infusion, opiate receptor activation and morphine actions. Studies have shown that the granuloma is not an infectious process.

Studies have suggested that morphine may activate lymphocyte activity (Chuang et al, 1997) and can initiate the inflammatory mediator nitric oxide. *In vitro* experiments have shown that prolonged exposure of immunocytes leads to an exaggerated response of monocytes to inflammatory stimulus. (Stefano, et al, 1995) Yaksh therefore proposes that morphine may activate inflammatory mediators within meningeal vasculature and initiate an increase in local capillary permeability to activated cells.

Yaksh and Malkmus ([354]) examined the effects of intrathecal morphine sulfate infused over 28 days in chronically catheterized dogs at a dose of 1 ml/day in concentrations from 1.5 to 12 mg/ml. They found a time and concentration-dependent increase in the severity of motor dysfunction (manifesting as increased hind limb motor tone). Histopathology revealed modest pericatheter reaction in <u>all</u> animals. At higher morphine concentrations, an inflammatory mass developed at the catheter tip producing a local compression of the spinal cord. This mass consisted of multifocal accumulations of neutrophils, monocytes, macrophages and plasma cells. At concentrations / doses of 12 mg/mL/day, <u>all</u> dogs displayed granuloma formation.

There have been several clinical case reports describing patients receiving chronic morphine infusion who present with a motor or sensory dysfunction secondary to a local compressive lesion. ([355];[356];[357];[358];[359];[360];[361];[362];).

Note that Sabbe et al ([363]) in 1994, found that the synthetic opioid sufentanil administered spinally in dogs, resulted in "an inflammatory reaction secondary to the catheter was found in all animals." This localised irritation may well give rise to more chronic inflammation in susceptible individuals.

Coffey and Burchiel ([364]) have looked at 41 cases of inflammatory mass lesions associated with intrathecal drug infusion catheters. They suggested a variety of hypotheses to account for this phenomenon, including: drug related mechanisms, infection, pyrogens, silicone hypersensitivity, and surgical trauma. Of these possibilities, they felt that the "use of relatively high-concentration, high-dose, or unlabeled analgesic drugs and admixtures is a plausible aetiology." They further suggested that delivery of these drugs might stimulate a chronic immune response around the catheter tip. The onset of the neurological symptoms in 23 patients

was characterized as sudden in 6 patients, sudden with prodromal symptoms in 2 and slowly progressing in 15.

Kamran and Wright ([365]), writing about the complications of intrathecal drug delivery systems, fail, as do the majority of authors, to adequately address the issues of long-term adverse effects. They refer to incidences of reduced libido and impotence of 6.1%, constipation 16.5% and peripheral oedema 5.1%; they also mention granuloma, seroma and infection. However, they do not discuss the longer-term sequelae to these problems, of which arachnoiditis may be one.

Jones et al. ([366]) reported on an outbreak of serious neurological complications associated with the inadvertent administration of morphine preparation that also contained methadone, or, in one case, traces of ethanol. 8 patients out of a practice of 61, (and out of 13 who were on morphine pump rather than other drugs) during one 4-week period developed complications such as sterile abscesses, and were left with new neurological deficit including paralysis. The authors attributed this outbreak to "Medical errors in an outpatient pharmacy."

As explained earlier, there are a variety of adverse effects that can arise from the intrathecal delivery of narcotics, as with any drug. (Note: only preservative free solutions are licensed by the FDA).

In 1999, Brown et al ([367]) looked at the outcomes of using the pump for a variety of conditions. The authors reported:

"Intrathecal opioid treatment provides some benefit although substantial physical impairment continues to cause debilitation in the patient population."

They conclude: "Generally, patients after 3 years or more of intrathecal opioid treatment can be characterised as having substantially impaired physical functioning with a high prevalence of side effects."

These ongoing side effects include:

- Reduced libido
- Pruritus (itching)
- Hyperalgesia (paradoxical increase in pain)
- Myoclonus (involuntary jerks)
- Urinary retention
- Amenorrhoea (discontinued periods)
- Uncommonly: raised antidiuretic hormone causing oedema in the lower limb
- Constipation

The use of adjuvants in the pump, such as clonidine, is becoming more widespread, despite a warning by the manufacturer of Duraclon stating clearly that it does not recommend intrathecal administration([368]). Epidural clonidine has been found to be helpful in combating neuropathic pain and was initially used in terminally ill patients. It is preservative free. Clonidine acts at a spinal level to produce analgesia. It was

first used clinically for this purpose in 1984. Gordh ([369]) from Sweden, in reviewing 15 years of what he terms " long term medication of the spinal cord" noted that its use for post-operative pain might be limited if it were used as a single agent, as doses sufficient to provide adequate analgesia also produce "troublesome side effects" including hypotension and bradycardia. He expressed doubt as to clonidine's useful role in post-operative pain management. However, he did cite its use in treating neuropathic cancer pain. In conclusion, Gordh remarked, "It may also be useful in chronic non-malignant pain, but large scale use in this field can hardly be recommended before results from controlled long term studies are available."

The UK based Development and Evaluation Committee Report ([370]) No.55 (June 1996) suggested that 30-50% of patients report 'excellent' pain relief. However, there is a warning:
"There are significant risks and complications with these devices."

See below, under Treatment for further information on INA adverse effects.

INTRATHECAL BACLOFEN:
This treatment is being used for children with severe spasticity due to conditions such as cerebral palsy. Intrathecal injection of baclofen (Lioresal) is clearly denoted as 'Not recommended' for use in children in the British National Formulary ([371]).
Baclofen was approved by the United States FDA in 1996 for the use in Medtronic pumps, to treat "cerebral spasticity". Previously trials of up to 41 months had been undertaken and reported efficacy and safety in adults with spinal spasticity ([372]). However, more than one study noted frequent complications: Ordia et al ([373]) reporting catheter-related problems occurring 19 times in 15 patients (out of 59 in the study), whilst Levin and Sperling ([374]) cited an "overall incidence of total complications" of 62% (24% with Infusaid pumps, 167% in Medtronic pumps). However, these studies were both in the mid90s, and the pump techniques and technology have improved somewhat since then.
In 1996, Albright ([375]) reported complications in around 20% of patients and infection necessitating pump removal in 5%.
In 1997, Armstrong et al ([376]) studied 12 children with a follow-up of 1-5 years. There were "favourable" results, although some central side effects. There were 10 mechanical complications, local infections in 3 children and meningitis in 2. The authors concluded:
"Results demonstrate the potential value of continuous intrathecal baclofen infusion for the treatment of severe spasticity of cerebral origin. However, this treatment can result in significant complications and more experience is required before the long-term benefits can be determined."

Rawicki's ([377]) paper in 1999 suggested that "Long-term continuous infusion of intrathecal baclofen delivered via an implantable pump offers an effective method for dealing with otherwise intractable spasticity." This emphasizes the point that cases in which this treatment is used are at the most severe end of the spectrum.

More recent studies have reported that Baclofen, administered intrathecally, is effective in managing the spasticity associated with cerebral palsy. In 2000, Gilmartin and colleagues ([378]) studied this in 44 patients who were followed up for up to 43 months. Adverse events occurred in 42 patients, although procedural/system problems were also reported as 59 events occurring in 30 patients. Adverse effects included hypotonia, seizures, somnolence and nausea/vomiting.

A study published in February of 2001([379]) evaluated the baclofen pump in treating spasticity in adolescents and adults with cerebral palsy. After one year, all the patients had some improvement. The authors noted that the side effects common after an oral dose (drowsiness and confusion) were reduced by the spinal delivery of the drug. A recent small study ([380]) found that whilst the Ashworth scale showed a substantial decrease in spasticity in the upper and lower extremities at 6 months, there was no evidence of functional change. Most treatment goals were at least partly achieved and carers reported that there were "improvements in comfort, function, and ease of care". However, "During 80 recipient-years of pump operation, 153 treatment-associated adverse events occurred: 27 of these were device-related." This sort of result again suggests that much closer attention should be paid to the longer-term effects of this type of treatment.

The Cochrane review in 2000([381]), cited 2 studies that had demonstrated a significant effect of intrathecal baclofen(ITB) in reducing spasticity due to spinal cord injury, but concluded, having reviewed several studies on the various antispastic agents, that "There is insufficient evidence to assist clinicians in a rational approach to antispastic treatment for SCI. Further research is urgently needed to improve the scientific basis of patient care."

CHEMONUCLEOLYSIS

Chymopapain, an enzyme that has been used for chemonucleolysis in treatment of prolapsed discs, also has been implicated in causing epidural fibrosis ([382]) and animal studies show severe nerve damage if injected into the nerve sheath ([383]). In fact, one paper suggests use of intrathecal chymopapain for use as a model for chemically induced spinal cord injury. ([384])

Chymopapain is a derivative of papaya, thought to react almost exclusively with nucleus pulposus of the disc when administered locally by injection. The aim is to dissolve extruded disc material thereby relieving compressed nerve roots. Reported incidence of allergic anaphylactic reactions to chymopapain is 0.3%.

Buchman et al ([385]) described a case of "hemorrhagic encephalomyelopathy followed by clinically suspected acute arachnoiditis" as a complication of lumbar injection of chymopapain.

Grainger and Allison, in their textbook, "Diagnostic Radiology" (2nd. Ed.) Cite "chymopapain inadvertently entering the subarachnoid space" as a cause of "severe necrotizing arachnoiditis". ([386]) They also show images of a case of severe arachnoiditis following percutaneous discolysis with chymopapain. Axial CT scan after myelography showed matted nerve roots forming irregular filling defects within the thecal sac.

I note that Alexander, a doctor in the US Navy working in the Orthopaedic Centre at Oakland, remarks on the following contraindications for chemonucleolysis ([387]): cauda equina syndrome, Failed Back Surgery Syndrome, sequestered disc fragment, spinal instability, severe spinal stenosis and of course allergy to

chymopapain. Alexander also suggests, "The overall incidence of neurologic complications is about 0.05%", basing this on cited articles ([388],[389]) as well as his own previous clinical experience ([390]).

INTRASPINAL CHEMOTHERAPY FOR CANCER

Patients with breast cancer that has metastasised to the meninges may now be treated with DepoCyt, a slow-release formulation of the cytotoxic drug, cytarabine. This treatment has been reported in studies published in October 2000([391]) and January 2001([392]). Both report encouraging therapeutic benefit in combating neoplastic meningitis in breast cancer, but cite arachnoiditis as one of the major adverse effects: 19% in one study, of which 88% were Grade 1 or 2 and "chemical arachnoiditis (i.e. headaches, fever, nausea, vomiting) was common". Despite a probably low survival (1 year survival projected as 19%) and the need for fewer injections (about a quarter the number needed in 'conventional' therapy) one must register concern as to the high incidence of arachnoiditis and the potential longer-term effects for those survivors.

In May 2002, doctors from Florida published a paper ([393]) on an open label trial of DepoCyt for the intrathecal treatment of solid tumour neoplastic meningitis. They found that grade 3 or 4 arachnoiditis occurred on 6% of treatment cycles, and reported: "The most important adverse events were headache and arachnoiditis."

METHOTREXATE:

Whilst MTX is clearly an important drug in the management of serious (rheumatoid arthritis) and sometimes life-threatening conditions (leukaemia, sarcoma), it does carry substantial risks of toxicity, especially to the liver, kidneys and nervous system, which can prove fatal. Current practice of intense triple chemotherapy has dramatically improved remission and survival rates from Acute Lymphoblastic Leukaemia (ALL), a lethal childhood leukaemia. Early implementation of central nervous system 'sanctuary therapy' is critical in preventing CNS relapse. Obviously this life-saving treatment is vital, but the risk of arachnoiditis developing later should be borne in mind when assessing longer-term outcomes. Chronic toxicities include leukoencephalopathy and a range of behavioural, neurophysiological and neuroendocrine disturbances.

Brain et al in 1997, ([394]) in Dijon, France noted that intrathecal methotrexate (MTX) caused cerebral toxicity: acute, subacute and delayed, as well as a chronic delayed leukoencephalopathy if used in conjunction with intravenous MTX and cerebral irradiation. They cited a case of a 21 year old patient who developed subacute encephalitis and arachnoiditis following administration of intrathecal (i-t) MTX to treat osteosarcoma.

Koh et al, ([395]) in Los Angeles, described "progressive paraplegia" and anterior lumbosacral radiculopathy after i-t MTX.

Lovblad et al described methotrexate encephalopathy with seizures ([396]), whilst Rubnitz et al ([397]) quantified the risk of transient focal neurological deficits in children with ALL given intravenous and intrathecal methotrexate as around 3%.

A Finnish group ([398]) noted, "Chemical arachnoiditis is known to be associated with intrathecal methotrexate therapy in children with leukaemia."

They were looking at collagen in the spinal fluid, which can be affected in ALL. The authors noted that there is a fibroproliferative response to inflammation in the arachnoid, which is related to concentrations of a certain type of procollagen. They postulated that administration of steroids might help to reduce this response and prevent development of adhesions in the arachnoid.

A Dutch group([399]) later looked at cells in the spinal fluid; they found an increase in protein levels in the CSF and increased cell numbers which they attributed to arachnoiditis due to MTX therapy a few days earlier.

Further adverse effects were noted in the Indian Journal of Radiology and Imaging ([400]): "paresis, paraplegia and chemical arachnoiditis".

Intrathecal treatment is also used for central nervous system prophylaxis in Non-Hodgkin's lymphoma.

CONCLUSION:

As Staats et al, in 1999 ([401]) described, "Spinal cord or nerve root toxicity may manifest itself as histologic, physiologic, or behavioural/clinical derangements after exposure to a spinal drug."

They maintain that "the neurotoxicity of spinal drugs is a central safety issue. ...We hope that this review stimulates future research on spinal drugs to follow a systematic approach to determining potential neurotoxicity."

In England, Jolles, Sewell and Leighton, at the National Institute for Medical Research, published a paper on "Drug-induced aseptic meningitis (DIAM): diagnosis and management" ([402]) and noted that intrathecal agents were (unsurprisingly) in the major categories of causative agents. They also remarked, "there appears to be an association between DIAM and connective tissue disease, particularly systemic lupus erythematosus, and ibuprofen." It is worth noting also that many patients who have rheumatoid arthritis may thus be at higher risk of developing chemical meningitis and possibly the chronic sequela of arachnoiditis, if intrathecal drugs are administered.

Hodgson et al., in their 1999 paper ([403]), conclude: "Overall, most spinal drugs in clinical use have been poorly studied for spinal cord and nerve root toxicity."

INADVERTENT EPIDURAL INJECTION

Kasaba et al. ([404]) looked at the experiences of anaesthetists in Japan. They found that 15(54%) had an experience of inadvertent epidural injection, and 5 of them had two experiences. These included: ephedrine (6 times), a mixture of neostigmine and atropine (3), thiopental (2), etilefrine (2), vecuronium (1), suxamethonium (1), bicarbonate (1), midazolam (1), lactated Ringer's solution (1), nicardipine (1), and pentazocine (1). The inadvertent injection of thiopental or bicarbonate was noticed by back pain during injection. Whilst no adverse events were reported, this type of incident can lead to longer-term problems, as

Hew et al. noted: ([405]) "Inadvertent administration of non-epidural medications into the epidural space has the potential for serious morbidity and mortality."

CHEMICALLY-INDUCED ARACHNOIDITIS (CIA) Vs MECHANICALLY INDUCED ARACHNOIDITIS (MIA)

Chemically-induced arachnoiditis tends to be more diffuse and cause more florid, systemic problems than mechanically-induced arachnoiditis, which is usually more localised and causes the expected neurological problems associated with pathology at the affected spinal level.

However, most patients will have some degree of both subtypes. There are a few who have purely MIA and a somewhat greater number who have arachnoiditis after chemical insult, without a history of trauma or surgery (or indeed a significant mechanical factor).

Chemically induced arachnoiditis (CIA) is essentially a toxic condition, which seems to involve a chronically-hypersensitised CNS, with substantial autonomic effects and centrally-originating pain.

This chronic "red-alert" situation then seems to trigger autoimmune problems, presumably via neuroimmunomodulation. There are similarities between CIA and MCS (Multiple chemical sensitivity); also, Human Adjuvant disease, Gulf War Syndrome.

MISCELLANEOUS AETIOLOGIES

Meningitis as a precursor of arachnoiditis:

As we have seen, arachnoiditis is inflammation in the meninges. The acute, better-known form is meningitis, which simply means inflammation of the meninges (not specifying which layer). Generally, the term is recognised as referring to an acute, sometimes life-threatening condition, usually caused by infection. Cases in children understandably hit the headlines. Bacterial meningitis, particularly meningococcal, is severe and can cause serious longer-term problems.

However, there may be more subtle sequelae, of which arachnoiditis is one.

Meningitis can therefore be regarded as a trigger event and it is thus important to look at features in different types of meningitis, so that the individuals who experience the illness can be recognised as being at risk of later developing arachnoiditis.

There are 2 types of meningitis anatomically speaking:

1. Leptomeningitis: involving the pia and arachnoid
2. Pachymeningitis involving the dura.

Meningitis can also be classified as:

1. Cranial

2. Spinal

Or:

1. Infective

2. Aseptic (non-infective)

Aseptic meningitis used to include viral meningitis.

Kioumehr et al. ([406]) characterised the patterns of cranial meningeal enhancement in post contrast MRI images. Leptomeningeal (pia and arachnoid): enhancement followed the contours of the cerebral gyri etc. and/or involved meninges around the basal cisterns. Pachymeningeal (dural) involved linear, thick enhancement or nodular, but not extending into the gyri or involving the basal cisterns.

The authors divided the enhancement into 5 aetiological groups: carcinomatous, infectious, inflammatory (secondary to collagen vascular disease or acidosis), reactive (post-traumatic, post-surgical) and chemical (rupture of cysts, intraspinal injections). There were 83 subjects, of whom 30 had carcinomatous, 28 infectious, 14 reactive, 8 chemical and 3 inflammatory aetiology.
83% of the carcinomatous, 100% of the reactive and inflammatory, 12% of chemical subgroups demonstrated pachymeningeal enhancement, whereas 100% of the infectious and 78% of the chemical subgroups had leptomeningeal enhancement.
The authors suggested that the variation in appearance might be helpful in distinguishing between infective and non-infective meningitis.

<u>Neoplastic meningitis:</u>

This term refers to meningitis associated with cancerous conditions. It occurs in about 5% of all patients ([407]) with cancer, and affects the entire neuraxis.
This type of meningitis carries a very poor prognosis: treatment is palliative with an expected median patient survival of 2 to 6 months. Kim and Glantz ([408]) noted: "Currently, the diagnosis occurs generally after the onset of neurologic manifestations and heralds a rapidly fatal course for most patients. By the time symptoms appear, most tumors have disseminated widely within the CNS, due to cortical irritation, compression of nervous system structures, or obstruction of CSF flow".
However, treatment of neoplastic meningitis may improve survival times.
Chamberlain et al. ([409]) looked at complications associated with intraventricular chemotherapy in patients with leptomeningeal metastases, arising from a variety of primary cancers. 52 out of 120 (43%) patients had aseptic/chemical meningitis, making this by far the most common complication.
New drugs such as intrathecal topotecan carry severe side effects including arachnoiditis. Blaney et al. in Texas ([410]) found "Arachnoiditis, characterized by fever, nausea, vomiting, headache, and back pain, was the dose-limiting toxic effect in two of four patients enrolled at the 0.7 mg dose level." They are now looking at a Phase II trial in children with neoplastic meningitis.
Chamberlain ([411]) found that intra-cerebrospinal fluid alpha-interferon was associated with toxicity,

"manifested as transient chemical arachnoiditis (16 out of 22 patients; 60% of all treatment cycles)" and concluded that it caused "considerable toxicity at the dose and schedule used in the current study and, as a result, may prove difficult to administer."

As with leukaemia, advances in treatment may well significantly improve life expectancy in these patients. However, arachnoiditis as a long-term sequela must be borne in mind during follow-up.

Infective causes:

Swiss authors Steinlin et al. ([412]) described 2 cases of children who had neonatal Escherichia Coli meningitis who later developed spinal granulomatous adhesions causing severe spinal complication in adolescence. One boy died after surgery for a high cord lesion, the other had severe progressive neurological deterioration with spinal and cerebella symptoms. The authors concluded that chronic arachnoiditis could occur many years after the acute bacterial meningitis.

Rosetti et al. ([413]) described 2 unusual cases of eosinophilic arachnoiditis. These tend to arise in immunocompromised patients, but in these cases, the patients were HIV-negative. They developed "cystic arachnoiditis over the spinal cord associated with eosinophilic meningitis". Histology of the meningeal spinal cord lesions showed a "vasculocentric mixed inflammatory reaction". Lacking any other explanation, the authors suggested the cases, in drug addicted patients, were caused by: "hyperergic reaction in the meniges (sic) toward drug-adulterants inoculated through the intravenous route."

Moling et al. ([414]) reported a case of cerebral aspergillosis, which tends to occur in severely immunocompromised patients. The patient presented with 14 months of chronic meningitis, ventriculitis, choroid plexitis and lumbar arachnoiditis, complicated by acute hydrocephalus. Aspergillus, from the candida group, was isolated from CSF.

Cystercicosis is the most common parasitic disease affecting the nervous system. It tends to arise through ingestion of contaminated water or food containing Taenia solium. More commonly, (60-90% of cases) the brain is affected, especially at the base of the brain where cysticerci accumulate in multicast or grapelike structures. However, in rare cases, the spinal cord is involved.

Colli et al. ([415]) reported on 12 cases of intradural spinal neurocysticercosis. Of these, 9 also had hydrocephalus, and developed nerve root symptoms some months later. In 9 cases, the lesion was in the thoracic or lumbar region, with 3 cases in the cervical region. Presenting symptoms included muscle weakness (67%), pain (67%) and sphincter disturbance (25%). These were in addition to symptoms corresponding to intracranial hypertension (headache, vomiting, transient visual loss, diplopia, and ataxia). The prognosis was worse for patients with moderate to severe arachnoiditis.

Sotelo and Marin ([416]) looked at 92 cases of hydrocephalus secondary to cysticercotic arachnoiditis. They found that mortality rate was around 50% within the first 2 years after shunting; and in most patients, arachnoiditis and positive immune reactions persisted for many years.

Recently, Arriada-Mendicoa et al. ([417]) described imaging features of sellar cysticercosis, which can cause extension through the basal cisterns and third ventricle with focal arachnoiditis arising as an inflammatory response. Cases may present with unexplained loss of visual acuity and hormonal disturbances.

Cosan et al. ([418]) presented a rare case of spinal toxoplasmosis, which initially manifested some 13 years before admission as a spastic paraparesis. Investigations showed that the patient had adhesive arachnoiditis associated with osteoid formation caused by past toxoplasmosis infection.

A case of proliferative granulomatous arachnoiditis as a form of tuberculous myeloradiculopathy was described by Amorin Diaz et al. ([419]). Of note, the authors remarked that autopsy revealed more extensive lesions than those imaged on serial MRI. Characteristic intramural inflammatory exudate with medullar necrosis was observed.

Poon et al. ([420]) in Hong Kong, recently reported a case of spinal tuberculous arachnoiditis after meningitis, with acute hydrocephalus. The patient had weakness of both lower limbs and urinary retention.

Recently Tanriverdi et al. ([421]) reported 3 cases of intradural spinal tuberculosis, which involved diagnosis of intramedullary abscess in the first case and early and late phases of arachnoiditis in the other two patients. The patients with arachnoiditis, who were treated by shunting or simple decompression, had a "relatively less favorable clinical outcome."

De at al. ([422]) published an article in the Journal of Indian Medicine in 2002, dealing with tuberculous meningitis (TBM) in children. The incidence of TB remains high in India, especially within slum areas, despite a routine vaccination programme. TBM has been considered as primarily a disease of young children (and the elderly). The authors described a 76% incidence of hydrocephalus with their study population (compared with 78% in Paginini and Gonzalez).

The authors recommended use of CT scan to diagnose the disease, "The triad of CT features (thalamic infarction, basal cisterns enhancement and hydrocephalus) is diagnostic of TBM." Other common features include enhancement of basal cisterns, periventricular lucency, tuberculoma and tuberculous abscess.

Boukobza et al. ([423]) described MRI features of CNS TB. These included: tuberculomas leptomeningitis, infarction, abscesses, hydrocephalus, and pachymeningitis. "A tuberculomas-leptomeningitis association was found in 4 patients. Patients with leptomeningitis showed thick meningeal contrast enhancement involving all basal cisterns, expanding to the sylvian fissures level, and causing narrowing of the sylvian arteries... In three out of five patients, leptomeningitis was the initial presentation."

Spanish authors Vega et al. ([424]) reported on 2 cases of tuberculous meningitis in patients with HIV, in which arachnoiditis ('radiculomyelitis') arose as a complication. Clinical presentation involved subacute paraplegia, radicular pain, sensitive level and neurogenic bladder.

Lyme disease: French authors Mantienne et al. ([425]) reported on a case of Lyme disease of the spinal cord, presenting as conus medullaris syndrome. They suggested that vasculitis was the likely mechanism for meningitis: "Leptomeningitis may be the first stage of spinal infection in Lyme disease, preceding parenchymal infection leading to myelitis". MRI findings were non-specific, showing contrast enhancement on the pial

surface in the lower thoracic cord and conus medullaris. Diagnosis was achieved via analysis of CSF which showed raised immunoglobulins against the organism Borrelia burgdorferi.

Coccidioides immitis is a fungus that primarily causes meningitis, typically widespread, especially involving the basal meninges. This chronic inflammatory response, a combination of suppurative and granulomatous inflammation, leads to thickening of meninges, hydrocephalus, arteritis, cranial nerve palsies and infarction. Other fungi (Blastomyces, histoplasma) may also cause meningitis.

Relapsing bacterial meningitis is a rare problem, mostly seen in neurosurgical patients. ([426]) Tang and Chen found that "Gram-negative bacilli, especially Klebsiella species, were the commonest micro-organisms identified for both the initial episode and the relapse of infection."

Nardone et al. ([427]) recently reported a case of symptomatic syringomyelia, which appeared six years after Listeria meningoencephalitis. They remarked: "Chronic spinal arachnoiditis, as shown by standard MRI and dynamic phase contrast (PC) cine-MRI, may occur after spinal infection and is likely the cause of syringomyelia."

Cases of iatrogenic infection have been reported after myelography, epidural injection, lumbar puncture and spinal surgery. Schneeberger et al. ([428]) noted: "Iatrogenic meningitis following lumbar puncture is a rare complication of myelography, spinal anesthesia, intrathecal chemotherapy, and epidural anesthesia."

Worthington et al, ([429]) described 2 cases of bacterial meningitis due to streptococcal infection after Iophendylate (Pantopaque) myelography. They suggested that it is difficult to differentiate from the "more common" aseptic meningitis arising after myelography.
Schelkun et al. reported another similar case. ([430])

Gelfand and Abolnik ([431]) suggested, "Bacterial meningitis is a rare complication of myelography". Again, it was noted that a distinction between chemical and bacterial meningitis might be difficult. They described three patients with streptococcal meningitis following myelography performed using the water-based contrast medium iopamidol.

More recently, Schlegel et al. in France ([432]) reported a case of iatrogenic meningitis due to the organism Abiotrophia defectiva after myelography.

Koka and Potti ([433]), reporting a case of abscess after epidural steroid injection wrote, "Although spinal epidural abscess is uncommon, its incidence is likely to rise with increasing use of epidural injections for the control of lower back pain."
There have also been reports of chemical meningitis ([434][435])
Kaiser et al. ([436]) reported a case of meningitis after spinal anaesthesia for hysteroscopy. Whilst they conjectured that this might have arisen as a result of a bacteraemia, they also suggested, "Contamination

from the patient's skin and from the upper airway's flora of the operator seems to be a more plausible cause." They also noted that spinal anaesthesia is contra-indicated in the febrile patient and concluded: "Asepsis is essential during spinal puncture".

Swedish author, Moen, ([437]) reported on 9 cases of iatrogenic meningitis, 8 after spinal anaesthesia and one after myelography. Alpha-haemolytic streptococci were cultured in seven cases, the remaining two cases being culture-negative. This organism is usually commensal, but has been implicated in cases of iatrogenic meningitis. It lives in the upper respiratory tract, which has lead several authors to recommend good hygiene and use of face masks as preventive measures during invasive spinal procedures. Indeed, Moen, remarking on a "widespread habit of omitting face masks when performing dural puncture", stresses, "The use of face masks should be mandatory whenever any kind of lumbar puncture is performed."

Trautmann et al., a German team, described 3 cases of bacterial meningitis ([438]) after spinal or epidural anaesthesia and noted that the organisms involved were likely to have come from the anaesthetist as a source of infection. Again, they emphasised the need for hygiene measures.
Recently, Couzigou et al. ([439]) once more stressed the need for "standard precautions" to avoid iatrogenic streptococcal meningitis after spinal anaesthesia.

Lovstad et al. ([440]) looked at intraspinal infections (meningitis and epidural abscess) as a complication of epidural analgesia. They described 3 well documented cases of meningitis and one with epidural abscess; of particular note is the delayed diagnosis in the patient with abscess because of 3 negative MRI scans. Infective organisms were from skin (Staphylococcus) or were opportunistic (Pseudomonas, Enterococcus, Micrococcus sp.). 2 patients were noted as being at risk "because of probable immunosuppression and chronic infections". The authors concluded:
"Because of the danger of infection related to epidural analgesia, all patients have to be properly monitored as long as they have epidural catheters and also after the removal of catheters. Some epidural abscesses spread longitudinally and may present as a diffuse process on MR without mechanical compression of the medulla, and may be interpreted as negative findings. Myelography with CT scan is an alternative method of investigation in such cases."

Epidural catheters are a source of infection: Shintani et al. ([441]) reported a case of acute epidural abscess and septic meningitis due to a contaminated catheter used in epidural anaesthesia. Methicillin-resistant Staphylococcus aureus (MRSA) was cultured. MR imaging showed a low intensity mass lesion compressing the thecal sac; this was likely to be pus with some gas component.

Holt et al. ([442]) studied 78 patients with culture-positive epidural catheters at Odense University Hospital in Denmark. 59 had symptoms of exit site infection and 11 had meningitis (2 also had epidural abscess), corresponding to an incidence of over 4% for local infection and 0.7% for central nervous system infection. The Gram-negative bacilli and Staphylococcus aureus caused serious infections more frequently than the others.

Use of the intrathecal pump for infusion of baclofen has also been associated with Staphylococcal meningitis. ([443])

Chemical Meningitis

A number of cases in the Global survey had a history of one or more episodes of chemical meningitis preceding their arachnoiditis.
Some authors in fact refer to episodes as chemical arachnoiditis.

Jolles et al. at the National Institute for Medical Research, London, ([444]) discussed Drug-induced aseptic meningitis (DIAM), which they denoted as "uncommon." The authors remarked that most of the literature comprises anecdotal case reports. The major types of causative drugs are nonsteroidal anti-inflammatory drugs (NSAIDs), antimicrobials (antibiotics) "intravenous immunoglobulin, intrathecal agents, vaccines". The authors also noted the association between lupus and DIAM and the link with ibuprofen. They stated that up to 60% of patients with SLE are estimated to have CNS symptoms associated with inflammation at some time during their illness, and that this could predispose them to DIAM.
They postulated 2 possible ways in which DIAM arises:
1. Direct irritation of the meninges by intrathecal administration of the drug, and
2. Immunological hypersensitivity to the drug.

In regard to intrathecally-administered drugs, Jolles noted that direct meningeal irritation might manifest itself several weeks after administration of the drug. Toxicity is related to concentration, lipid solubility, particle size, ability to ionise the CSF and duration of contact with CSF.
Notably, Jolles remarks on the need to consider injection of substances other than the suspected drug, such as anaesthetic, diluent or contaminant. To that I would also add preservatives, as already discussed.
The paper goes on to note the numerous reports relating to myelography contrast media, both oil and water-soluble, precipitating acute meningitis ([445];[446]). This may cause clinical symptoms within hours or delayed by as much as 2 weeks.

Various authors have reported cases of chemical meningitis due to myelography dyes. Vik-Mo and Maurer ([447]) in 1975 suggested that severe acute meningeal reactions after lumbar myelography could be due to contamination of the spinal fluid with a detergent-washing agent.
However, other authors attributed the meningitis directly to the dye: Worthington et al. ([448]) reported a case of acute chemical meningitis after metrizamide myelography; Sand et al. ([449]) described 7 similar cases.
Worthington and colleagues remarked that whilst "rare" these cases warranted being "followed carefully for possible later sequelae."
White ([450]) described a case of metrizamide meningitis arising 24 hours after myelography and presenting

with fever, nuchal rigidity, vomiting, and mental confusion. Spinal fluid cultures were negative.

In 1985, DiMario reported on a case of aseptic meningitis secondary to metrizamide in a small infant (age 4 and half months). ([451])

In Belgium, a case of meningitis following iohexol was reported in 1991([452]). Iohexol was a popular and widely used water-based dye that largely replaced older ones and was regarded as safe.

Norwegian authors Bo, Nestvold and Sortland ([453]) also described 2 cases of meningitis following iohexol used in the mid-1990s. As the previous authors, they remarked that clinically the presentation was indistinguishable from that of bacterial meningitis.

Forgacs et al. ([454]) noted a series in The Netherlands that found a 3% incidence of bacterial meningitis after transphenoidal surgery. They also noted that drugs administered to microsurgical patients can cause chemical meningitis. These included: NSAIDs, antibiotics (sulphonamides, penicillins) gamma globulin and OKT3. Comparing infectious and non-infectious causes, the authors looked at 70 consecutive patients with post-operative meningitis, of which 27 met the criteria for chemical meningitis (negative spinal fluid cultures and patient recovery without antibiotics), 13 bacterial and 20 were "indeterminant". Cases of chemical meningitis showed raised white cell count in the CSF (but <7500) and glucose >10mg/dL). They rarely had temperatures above 39.4°C and fever was of shorter duration than with infective meningitis. They concluded that sterile meningitis is more common after posterior fossa surgery.

Other agents causing chemical meningitis include: gadolinium ([455]), baclofen ([456]), methotrexate ([457]), cytarabine: both systemic and intrathecal, ([458] ;[459]).

Recently, French authors Hoeffel et al. ([460]) reported a case of chemical meningitis after intrathecal injection of contrast media and hydrocortisone. (They also described a case of intracranial haematoma after intrathecal injection of 125 ml of hydrocortisone acetate).

Intrathecal injection of steroid preparations, either methylprednisolone or hydrocortisone ([461] ;[462]) can cause chemical meningitis. Plumb and Dismukes ([463]) suggested: "Steroid-induced chemical meningitis should be considered in any patient who develops CNS symptoms and an abnormal CSF after receiving intrathecal steroids."

Spinal anaesthesia may also cause chemical meningitis; various factors such as contaminants in the preparation, disinfectant, starch (in sterile gloves) have been implicated. ([464])

In 1999, Lakhkar and Sinha reported in the Indian Journal of Radiology and Imaging, a case of a 6 year old boy treated for acute lymphoblastic leukaemia with intrathecal methotrexate, who developed hemiplegia and seizures due to an intracerebral bleed. The authors noted that "transient" complications of IT-MTX

include paresis, paraplegia and chemical arachnoiditis.

Also in 1999, Fukushima et al. ([465]) reported a case of chemical meningitis in a child undergoing CNS prophylactic treatment for acute lymphoblastic leukaemia. MR imaging showed diffuse pachymeningeal enhancement.

Inadvertent intrathecal injection of vincristine causes leptomeningitis and ventriculitis ([466]) that in some cases if fatal. Cerebrospinal lavage must be undertaken to reduce the damage. Surviving cases may go on to have long-term problems as a result of the toxicity.

Other cases of aseptic meningitis can also arise.

Collard et al. ([467]) reported a case in a patient with familial Mediterranean fever (FMF), who had 6 episodes of aseptic meningitis within a 7 year period.

Mollaret's meningitis is a rare phenomenon, first described in 1944. It refers to chronic recurrent aseptic meningitis, usually of unknown aetiology. Thilmann et al. described ([468]) 2 cases of recurrent aseptic meningitis, one of which had an initial episode after myelography with iopamidol, and a second after oral ingestion of the NSAID ibuprofen (400mg). Indeed, ibuprofen has been reported a number of times as a cause of aseptic meningitis, especially in patients with Systemic Lupus Erythematosus; Horn et al. reported a case in a patient with rheumatoid arthritis ([469]), Pisani et al. ([470]) described 3 episodes over a period of 20 years, in an otherwise healthy patient, after taking ibuprofen.
The patient described by Thilmann suffered 5 attacks of meningitis in total, 2 of which were drug-related, the other 3 arising spontaneously. Thilmann and colleague suggested that Mollaret-meningitis is a "special form of a drug-induced allergic reaction, the provoking agent of which remains unknown." As Horn and colleagues pointed out, this may be linked to autoimmune conditions such as lupus and may thus have a particular relevance in arachnoiditis. They concluded: "Although persons with systemic lupus erythematosus appear to have an increased risk for this type of reaction, the development of signs and symptoms in other patients warrants the consideration of nonsteroidal antiinflammatory drugs as the cause of aseptic meningitis."

Japanese authors Kohira and Ninomiya ([471]) described a case of Mollaret meningitis with back pain, where herpes simplex virus type 2 was found in the CSF. The 59 year-old woman had four episodes of recurrent self-limited aseptic meningitis, featuring acute headache, back pain, and nausea with fever, which resolved within 14-20 days.

Other causes of aseptic meningitis include events such as rupture of a pineal cyst ([472]) and intracranial epidermoid tumours ([473]).

Maignen et al. ([474]) suggested that various drugs (non-steroidal anti-inflammatory agents such as ibuprofen

and sulindac, antibiotics such as cotrimoxazole, trimethoprim, ciprofloxacin and miscellaneous drugs such as carbamazepine, human immune globulin and muromonab CD3) could be associated with development of aseptic meningitis, and those patients with lupus or connective tissue disorders are at a higher risk. They noted "Meningeal symptoms occur a few hours after drug intake and resolve without sequelae within one or two days after drug withdrawal."

Sarcoidosis

Sarcoidosis is an inflammatory disease, first identified over 100 years ago, which can affect almost any body organ, although it usually starts in the lungs or lymph nodes. The cause remains unknown, and the disease can appear and disappear suddenly, or develop gradually with fluctuating symptoms that can persist throughout life.

As the disease progresses, small lumps, termed **granulomas**, appear in the affected tissues. In the majority of cases, these granulomas clear up, either with or without treatment. However, in some cases, they do not remit and there is ongoing tissue inflammation that leads to scarring (fibrosis).

The USA National Institute of Health (NIH) notes: "Sarcoidosis is currently thought to be associated with an abnormal immune response. Whether a foreign substance is the trigger; whether that trigger is a chemical, drug, virus, or some other substance; and how exactly the immune disturbance is caused are not known." ([475])

CNS sarcoidosis has been reported in approximately 5% of patients with sarcoidosis ([476];[477])

Chronic leptomeningitis in the basilar cisterns and hypothalamic regions are typical manifestations of CNS sarcoidosis ([478]). Bahr et al. ([479]) looked at 6 cases of intracranial sarcoidosis and found that communicating hydrocephalus with sarcoid arachnoiditis is the most common finding, although arteritis and masses have also been reported. Kendall and Tatler ([480]) found that the spinal cord might be involved by intra-medullary granulomas or meningeal infiltration causing arachnoiditis. Leptomeningeal granulomatous infiltration manifests as an intense meningeal enhancement on gadolinium-enhanced T1-weighted images (enhancement of the basal meninges still suggests an active inflammatory process, whereas its absence suggests fibrosis ([481]) and may go unnoticed with unenhanced MR ([482]). The suprasellar and frontal basal meninges and the depths of the sulci are most frequently affected. Occasionally, granulomas coalesce to form mass-like lesions, particularly in the region of chiasm, floor of the third ventricle, and pituitary stalk ([483]). Hydrocephalus may be a complication of chronic meningitis.

Hosseini and Tourbah ([484]) described a case of sarcoid related optochiasmic arachnoiditis, presenting as bilateral visual loss, pain on eye movement and headache, developing rapidly within a few days. The patient had longstanding pulmonary sarcoidosis. CSF showed evidence of aseptic meningitis. Cranial MRI showed hypertrophy of the chiasma and of the cisternal portion of both optic nerves, a hypersignal on T2 weighted images and post-gadolinium enhancement on T1 weighted images. The patient improved on steroid treatment. Follow-up MRI 2 months later showed decrease in size of the affected nerves and loss of enhancement on T1 images.

Russian authors Makarov et al. ([485]) looked at neurosarcoidosis; they found granulomatous lesions in the central nervous system in 14% of patients with respiratory tract sarcoidosis. Clinical classification of neurosarcoidosis included specific granulomatous forms: CNS arachnoiditis and perivasculitis, sarcoid myositis, as well as non-specific forms (vasoautonomic dystonic syndrome, angiotrophoneurosis).
Willigers and Koehler in The Netherlands ([486]) described a case of a 20 year old woman, who presented with subacute amnesia. She was found to have neurosarcoidosis. There were several features: isolated bilateral temporal hydrocephalus, caused by ventriculitis / arachnoiditis as well spinal arachnoiditis as demonstrated by myelography, which, incidentally, was not noticed on MR scan.
Cooper et al. ([487]) reported a case of neurosarcoidosis with optic nerve involvement as well as two intracranial parenchymal lesions and granulomatous arachnoiditis. The authors noted that MRI offered no advantages over CT in the orbit but was significantly more accurate intracranially.

BLOOD IN THE SUBARACHNOID SPACE

Blood is a potent irritant to nervous tissue and alone can cause arachnoiditis. In combination with chemical substances, the risk is magnified. This was first noted in relation to oil-based myelographic dyes by Howland and Curry ([488]) who found that in dogs, blood and dye together caused severe adverse effects. Hence dural puncture during epidural administration of drugs should be treated seriously. Common practice currently involves administration of an epidural blood patch (EBP) which aims to seal the spinal fluid leak to reduce the impact of the post-dural puncture headache (PDPH). However this practice introduces the highly irritant blood into the delicate area of the subarachnoid space. (See above).

Arachnoiditis as a complication of subarachnoid haemorrhage:

This has been reported by various authors. Blood in the subarachnoid space is highly irritant. Aldrete has described the acute meningeal reaction followed by a chronic reactive process involving fibrosis and adhesions.
Tjandra et al. ([489]) gave a detailed report of two cases in which subarachnoid haemorrhage was later associated with chronic arachnoiditis, with progression to loss of spinal cord function and in one case, spinal cord cavitation causing paraplegia. Shaw et al. ([490]) noted that these complications seem to occur more frequently in the thoracic spine.
Jourdan et al. described a case of spinal arachnoiditis with paraplegia after subarachnoid haemorrhage due to a ruptured intracranial aneurysm. ([491])
Taguchi et al. ([492]) reported a case of spinal arachnoiditis and a spinal arachnoid cyst in a patient who sustained a ruptured vertebral artery aneurysm. The authors speculated that the use of fibrin glue during the reparative surgery might have been a causative factor in the formation of the arachnoid cyst.

In 2000, Kok et al ([493]) reported on two cases of spinal arachnoiditis after subarachnoid haemorrhage, in which there was complete spinal block at thoracic level. They noted that gradual improvement in symptoms occurred over a period of time.

Arachnoiditis following trauma or multiple lumbar punctures may also arise due to the presence of blood within the subarachnoid space.

Cases in children:

York and Devoe ([494]) wrote about health issues in surviving premature infants. They pointed out that premature birth (before 37 weeks) occurs in around 11.6% of all live births. Technological advances have increased the survival rate amongst premature babies. However, longer term morbidity should not be overlooked.

One of the risks in preterm infants is intraventricular haemorrhage, which York and Devoe suggest is reported in 35-50% of infants at less than 32 weeks' gestation or weighing less than 1,500g at birth. Indian authors Narayan et al. ([495]) found a 29% incidence.

This is related to fragility of capillaries and poor support of the vascular bed in premature infants. Depending on the grade of IVH (as defined by Papile), there is a potential for long term morbidity. In grade 4 haemorrhages, long-term sequelae are almost inevitable.

One of these consequences is post haemorrhagic hydrocephalus; the acute type arises either as a result of a blood clot impairing normal CSF flow, or obstruction of CSF absorption at the level of the arachnoid villi. Chronic hydrocephalus is caused by obliterative arachnoiditis or blockage from necrotic debris, reactive gliosis or disrupted ependyma (interfering with CSF flow).

Progressive hydrocephalus is associated with raised intracranial pressure and requires insertion of a shunt to relieve this. There are of course, a number of recognised shunt complications, which can contribute substantially to the long term morbidity.

Professor Andrew Whitelaw and colleagues at Bristol University recently looked at hydrocephalus after intraventricular haemorrhage. Whitelaw had also been involved with Cherian et al's rat study ([496]), which provided a model for post-haemorrhagic ventricular dilation. Cherian noted that IVH affects about 15% of all premature births. In babies weighing less than 1,000 g at birth, 10-20% have large haemorrhages that distend the lateral ventricles. Over half develop post-haemorrhagic ventricular dilation (PHVD); 60-80% suffer long-term neurological disability (note also that about 40% of adults who have a large intraventricular bleed develop hydrocephalus). The authors suggested that defective fibrinolysis in the CSF may be a contributory factor (Note Jayson's work on arachnoiditis). Haemorrhage seems to upregulate fibroblast activity within the subarachnoid space. It also impairs fluid drainage along perivascular spaces

within the brain and impedes passage of CSF through the subarachnoid space and arachnoid villi.
The rat study showed that the initial ventricular dilation in response to injection of blood can, and in some cases, does, initiate a progressive pathological process. The rats with more severe hydrocephalus had more severe gliosis.
Whitelaw et al. ([497]) piloted a new treatment called DRIFT, (drainage, irrigation with protein-free CSF, fibrinolytic therapy) aiming to reduce intracranial pressure and decrease inflammatory substances such as cytokines.
Whitelaw remarks that multiple blood clots may obstruct the ventricular system soon after the haemorrhage, "but lead to a chronic arachnoiditis of the basal cisterns involving deposition of the extra cellular matrix proteins in the foramina of the fourth ventricle and the subarachnoid space." He suggests that transforming growth factor beta (TGFβ) is a key mediator, as it is known to be involved with wound healing and fibrosis. TGFβ is raised in CSF of adults with post-haemorrhagic hydrocephalus.

Arachnoiditis may also be seen within the context of congenital spinal abnormalities such as dermal sinus tracts (DST). Ackerman et al. ([498]) described 9 cases of thoracic or cervical DST. In 4, there was "opacified arachnoid or frank arachnoiditis."

Surgical treatment of congenital spinal defects such as spina bifida, myelomeningocele, MMC (a neural tube defect), is associated with later development of arachnoiditis. MMC arises when the neural tube, the embryonic spinal canal, fails to close in the fourth week of gestation. In the 'two-hit hypothesis', this is the 'first hit', the 'second hit' being spinal cord injury as result of exposure of the uncovered cord to the amniotic fluid and CSF outflow through the defect.
MMC is the most common form of neural tube defect. The meninges protrude through a midline bony defect of the spine forming a sac containing CSF, with a flat plate of neural tissue. Often MMC is associated with other nervous system abnormalities such as Chiari II malformation.
Before neurosurgical treatment became established in the 1960s, MMC was usually fatal due to hydrocephalus, meningitis or other problems. Now 14% will survive less than 5 years (35% if there is associated Chiari II malformation).
Most babies with spina bifida have hydrocephalus at birth or develop it later and require shunting.
MMC surgical closure is associated with secondary tethering of the spinal cord. Wagner et al. ([499]) state: "primary MMC repair is inevitably followed by the development of arachnoiditis, fibrosis and adhesions between spinal structures." They suggest that about a third of patients develop symptomatic cord tethering, presenting as progressive scoliosis, gait changes, spasticity or pain, and less commonly with changes in bladder function, weakness and contractures in the lower limbs.
Whilst these symptoms can be alleviated by surgical dissection of the arachnoid adhesions, recurrence is common. Wagner and his colleagues state, "Different procedures for dural closure...have been described, but, to date, there is no effective method known to prevent retethering."
Spinal arachnoid cysts may develop.
40-80% of patients with MMC have intramedullary cavities (hydrosyringomyelia), which may be aggravated

by the cord tethering. Large or progressive cavities, which are more often found in older children or adults, may need to be treated surgically.

Other neurosurgical procedures can be associated with acute meningitis:
Carmel and Greif ([500]) described aseptic meningitis as a syndrome characterised by spiking fever and meningismus (signs of meningeal irritation such as stiff neck).They noted that an earlier series involved 70% of children with posterior fossa operations developing the syndrome, whilst a new review had put the incidence at slightly over 30%. Aseptic meningitis after operation on structural lesions was 44% (higher than in the tumour group).
As we have seen, meningitis can be a precursor of arachnoiditis.

Children with leukaemia are treated with cytotoxic agents, often administered intrathecally. Arachnoiditis is a recognized complication of this treatment (see above).

SYMPTOMS IN ADHESIVE ARACHNOIDITIS

IT MUST BE STRESSED THAT ANY PERSISTENT NEW SYMPTOM OR SUSTAINED INCREASE IN PAIN SHOULD BE CHECKED OUT BY A DOCTOR AND NOT ASSUMED TO BE PART OF THE ARACHNOIDITIS SYNDROME.

Overview:
Adhesive arachnoiditis presents with diverse symptoms, which can include problems outside the CNS. This can best be described as a neurological syndrome. However the treatments used for the pain and other symptoms also cause a variety of side-effects, so it is difficult to say exactly which symptoms can be directly and solely ascribed to arachnoiditis, and which are more complex in origin.

Primary: due to original spinal condition; and those attributable directly to AA;
Secondary: musculoskeletal, autonomic, etc.; those secondary to pain; side-effects of medication
Tertiary: depression, anxiety etc.

Long (vi) wrote: “The authors of all the major papers that describe chronic adhesive arachnoiditis conclude that the symptoms are so varied that none can be considered typical for arachnoiditis...the general consensus is that no typical syndrome exists.”

The medical literature mostly describes adhesive arachnoiditis in terms of symptoms referable to the spine, i.e. in the lower back and or legs, with pain, weakness and sensory loss. Some authors also discuss bladder and sexual dysfunction. Jenik et al ([501]) described the symptoms as "predominantly syringomyelic sensory deficits".

This type of description fosters the common perception of arachnoiditis as a spinal condition. However, in many cases, adhesive arachnoiditis is syndromic.

The Global survey in 1999, which gathered information from over 300 participants, found a wide range of symptoms. Overall, the common picture confirmed the syndromic nature of the condition. Individuals who had a history of chemical insult tended to develop more florid symptoms and repeated exposure to chemical insult resulted in severe illness, often with other conditions diagnosed alongside the arachnoiditis, most notably autoimmune disorders.

Other surveys by Aldrete ([502]) in America and Simpson and Anderson ([503]) in New Zealand have also helped to clarify the spectrum of symptoms seen in this condition.

One of the principle difficulties with arachnoiditis is that it is a complex situation, comprising most often an initial spinal problem such as disc disease, trauma etc. or some event such as meningitis. On top of this there may have been invasive investigations such as myelograms, then further procedures such as surgery, often multiple. Later there may well be more invasive interventions such as epidural steroids or even the 'pump'. These may overlie a continuing spinal abnormality, including degenerative changes such as stenosis.

Aside from these considerations, we must also bear in mind the deleterious effects of unrelieved chronic pain, which, contrary to some medical opinion, may have significant and widespread impact on the body as a whole, such as increased muscle tone, raised stress hormones as well as secondary effects such as insomnia and depression. These are not unique to arachnoiditis.

It is thus often more or less impossible to confidently attribute a specific symptom to the pathological process of arachnoiditis.

However, what is important is for clinicians and patients alike to develop a greater level of awareness of the typical problems one might encounter in symptomatic arachnoiditis.

It is worth noting that as a general proposition, the global survey findings suggested that the more severe or repeated the chemical insult, the more florid and systemic the resulting disease, often with concomitant conditions of an autoimmune nature.

This section of the article will attempt to clarify the range of symptoms that may be experienced in arachnoiditis. It must, however, be stressed that many people with arachnoiditis will not have some of these symptoms, especially the uncommon ones.

Spinal signs:

Aldrete states, "it must be kept in mind that the presence or absence of radiculopathy signs do not necessarily confirm or deny the diagnosis of ARC." (504)

This very important statement is at the heart of problems in patients being unable to get a definitive diagnosis, and the frequent dismissal of their problems as psychosomatic, or malingering, due to lack of clinical signs.

The ability of ARC to affect not only continuous areas, but also intermittent areas along a dermatome, can lead to confusion.

It is important to consider underlying spinal conditions such as spinal stenosis.
The chief symptom of stenosis is what is termed "neurogenic claudication"(from the Latin "claudico", meaning "I limp") which refers to lower limb pain, often bilateral, which comes on with walking or standing for a length of time. As the condition progresses, walking distance and standing time are progressively decreased. Symptoms are relieved by sitting down or bending forward (compare disc herniation, in which bending exacerbates the pain or facet joint pain which is worse on leaning backwards). Some patients will bend down or squat as if about to tie their shoe-lace, to relieve pain on walking and there is the "shopping cart" sign which is when a patient will lean over the back of the shopping trolley to relieve the pain of standing in a queue. Flexion of the spine reduces symptoms, whereas extension exacerbates them.
Neurogenic claudication should be distinguished from vascular intermittent claudication. The circulatory nature of the latter will present other features such as skin pallor or mottling, and impaired peripheral pulses. Significantly, resting in the standing position (unlike neurogenic claudication) relieves the pain of vascular claudication on exercise.
The pain tends to be burning, gripping or cramping in nature, and radiates from the buttocks down the leg. The patient may describe it as "vice-like". There may also be dull aching and fatigue in the thighs and legs. Other symptoms may include tingling and numbness, as well as a degree of weakness. In severe cases, urinary incontinence can occur. Low back pain may also be a feature, but not usually a predominant one.
A study by Jonsson et al (505) concluded that: "Pain was more intense and positive straight leg raising test results were more common in younger patients, whereas reflex disturbances were more common in the elderly."
It must be remembered that other spinal conditions may co-exist with stenosis, in particular, disc disease. This may complicate the clinical picture.

Aside from the local effects due to the arachnoiditis lesions and underlying spinal condition (e.g. degenerative disc disease), one must also take into account the effects of altered spinal dynamics: in protecting the affected spinal area, other areas are put under undue strain; a chronically abnormal posture may be adopted which results in thoracic and cervical complaints in addition to the lumbar pain. These biomechanical/postural effects are the commonest cause of widespread pain.

Bearing in mind that Jenik described arachnoiditis symptoms as principally syringomyelic and the current prevailing theories about syrinx formation (altered CSF flow dynamics) I have hypothesised that these upper body symptoms are, in some cases, due to abnormal CSF flow (in essence sub-clinical syringomyelia). It seems logical to suggest that scarring within the subarachnoid space will disturb CSF pressure in the enclosed system and that this will affect the entire cerebrospinal axis. This might also explain the headaches, which are reminiscent of those caused by raised intracranial pressure.

A further explanation is that in cases of CIA, especially after intrathecal injections such as Myodil, the chemicals may have travelled up and down the subarachnoid space to some distance from the injection site, and may therefore have a direct toxic effect on those areas. (E.g. some patients who had cervical myelograms with Myodil now have cerebral arachnoiditis as well as cervical).

Pain

"Pain is the most common symptom for which patients seek care." Markenson

Intractable Pain

This term originated in 1990, when Texas and California enacted "Intractable Pain" Laws, in which intractable pain was defined as:

"A pain state in which the cause of the pain cannot be removed or otherwise treated and which in the generally accepted course of medical practice no relief or cure of the cause is possible or none has been found after reasonable efforts."

These laws went on to be adopted by a number of other States, and aimed to permit physicians to prescribe controlled drugs such as narcotics.

The American Medical Association defines chronic pain thus:
"Chronic Pain is a self-sustaining, self-reinforcing, and self-regenerating process. It is not a symptom of an underlying acute somatic injury but rather, a destructive illness in its own right. It is an illness of the whole person and not a disease caused by the pathological state of an organ system. Chronic pain is persistent, long-lived, and progressive. Pain perception is markedly enhanced..."

Forest Tennant, director of Veract, an organisation dedicated to research into and treatment of intractable pain ([506]), uses the following definition:

"Pain that is excruciating, constant, incurable and of such severity that it dominates virtually every conscious moment, produces mental and physical debilitation and may produce a desire to commit suicide for the sole purpose of stopping the pain."

Dr. Tennant suggests an incidence of 2-5% of intractable pain in the general adult population. Amongst people with adhesive arachnoiditis, it is virtually 100%.

He furthermore asserts that IP, if untreated, is "an internal, systemic disease" that affects various parts of the body.

Poorly controlled (intractable) pain induces a state of constant physiological arousal (stress) resulting in elevated levels of the stress hormones adrenaline, insulin and cortisol in the blood stream. These are responsible for a wide variety of symptoms:

1. *Adrenaline:* high pulse rate, palpitations, raised blood pressure, anxiety, panic attacks, insomnia and also, at times when the levels become depleted, (often mid-afternoon), fatigue, headache, depression and low attention span. The autonomic imbalance towards the sympathetic nervous system overactivity is a common feature of chronic pain syndromes of all types.
2. *Insulin:* this hormone is involved with the regulation of blood sugar levels. Excessive secretion causes low blood sugar and weakness. It may be that prolonged excess levels eventually deplete the body of the capacity to manufacture insulin or are in some way involved in the development of antibodies to insulin (causing insulin resistance): and this development of diabetes mellitus.
3. *Cortisol:* this stress hormone is implicated in the development of osteoporosis, immune suppression; weight gain and fluctuating energy levels. It may also impact on electrolyte (sodium and potassium) levels in the blood.

Combined excess blood levels of these hormones can result in muscle pain/weakness and fatigue.

The predominant and most distressing symptom of arachnoiditis is chronic, persistent pain which is primarily neurogenic (nerve generated) and thus difficult to treat. All (100%) of patients in the Global survey had pain.

Compare this with the results of an NHS survey of cancer patients, in which 9% experienced pain or discomfort all of the time, 34% some of the time and 20% experienced severe pain.

This pain is transmitted from the dorsal root ganglia (DRG) in the spinal cord. In contrast to normal DRGs, inflamed DRGs produce sustained pain impulses from any mild stimulus such as body movements or even breathing. It is thought that pain receptors (nociceptors) become permanently 'switched on' when there is persistent pain and/or damage to the nervous system.

Pain tends to increase with activity. There may be a delay after onset of activity, with a slow summation (build up), to a point where the pain suddenly becomes unbearable and then persists once the activity has ceased. Quite often, there is no immediate effect of activity, and it is only on the following day that the symptoms are exacerbated, and they may well remain more severe than normal for days or even weeks. This can make it difficult for patients and physicians or physiotherapists to assess what is the tolerable level of exercise.

Pain may be due to other factors besides nerve damage. These include musculoskeletal sources secondary to disuse, overuse or compensatory use of muscle groups, due to alteration of spine dynamics. There may also be muscle tension due to being in pain, or increased muscle tone (spasticity) caused by nerve damage. This can be accompanied by pains in the joints.

Secondary effects of pain:

- Sleep deprivation
- Muscle wasting
- Joint stiffness
- Reduced activity/immobility
- No longer working
- Social isolation
- Financial struggle
- Low self-esteem/low mood

Types of pain

Aldrete looked at pain-related symptoms and found the following types:
Gnawing (lumbosacral): 46%
Constricting (legs or ankles): 26%
Stabbing (Lumbosacral): 24%
Burning: one foot: 55%; both feet 37%; lower back: 6.7%

Aldrete described the burning sensation in the feet and legs (88% of patients overall) as being a "pathognomonic feature" of arachnoiditis.

The New Zealand survey found the following types:

Type	Mild%	Moderate%	Severe%	**Total%**
Sharp	6	12	32	**50**
Dull	14	25	25	**64**
Burning	9	22	30	**61**
Stabbing	4	15	25	**44**
Electric shock	11	12	16	**39**
Constant	22	23	39	**84**
Intermittent	17	16	25	**58**

The pain is generally described as burning, but often people are unable to describe it. This type of pain is termed dysaesthesia (by definition indescribable, bizarre pain). It is not felt by normal people and is specifically a feature of incomplete nerve damage. It may sometimes be called deafferentation pain, or causalgia. Many patients suffer from burning feet, in particular.

The majority of patients also have transient shooting pains that may vary in intensity from an insect bite to an electric shock.

Persistent pain can affect the way in which the central nervous system functions, by inducing central sensitisation. This effectively means that the nervous system is in a constant state of 'red alert' and is hypersensitive to all incoming messages (stimuli).

Breakthrough pain is a transient flare of pain occurring against a background of otherwise well controlled pain. (See below)

Central pain:

Some of the sensory problems may be generated from centres higher than the spinal cord. This is called central pain, and is due to hypersensitivity of the central nervous system.

It occurs when injury to the central nervous system is partial, and thus causes central sensitisation in the absence of total loss of function or sensation. It is commonly seen in patients with spinal cord injury (SCI).

Tasker ([507]) includes various conditions in his classification of central or deafferentation pain, and amongst these he specifies arachnoiditis as a cause.

The classical form of central pain is characterised by a constant, severe burning, often with a paradoxical component of cold, made worse by light touch. In some variations, pain from movement or from muscle tone is the major feature. Recently, brain scans have revealed that the pain signal to the thalamus (the area of the brain that receives this input) may be severe enough to make it shut down to avoid cell death, which allows the uninhibited pain signal to reach the conscious brain.

Myers suggested in 1995 ([508]), "Ischaemic (poor blood supply) compression lesions may be the most common painful neuropathy" and noted that chronic constriction injury studies in rats cause hyperalgesia and allodynia in the distribution of the affected nerve. This is a form of deafferentation pain.
Many patients with arachnoiditis seem to suffer from pain throughout the body, in areas that do not correspond to the site of the arachnoiditis. Therefore, it seems that there may well be a component of central pain involved.
Devor, in 1995([509]), proposed that nerve damage causes pain by "injecting abnormal discharges into the nervous system". It is now widely thought that there is a form of "wind-up" of nerve cell firing, in which cells that normally do not deal with pain become pain receptors (nociceptors), which widens the area involved. This can induce a "pain memory" which may involve various systems within the CNS (central nervous system). (Coniam and Diamond, 1992[510]) The nociceptive input can generate within the spinal cord a state of "central sensitisation". Input into this is amplified. It also seems that the inhibitory system is affected the most by nervous tissue damage.
Central pain is recognised as being agonising. The brain is being bombarded with the same sort of information it would receive if severe tissue damage were occurring.

Mnemonic for central pain: **MD has CP:**

Muscle Pain (Gamma Pain)
Dysaesthesia
Hyperpathia
Allodynia
Shooting Pain (Lancinating)
Circulatory
Peristaltic Pain (Visceral)
([511])

MUSCLE PAIN: As well as the pain pathways discussed above, there is also the sensory arm of the gamma motor system, or pain sensation from the muscle spindle apparatus within the muscles. Just as pain in the skin, so both allodynic and hyperpathic pain can be associated with muscle spindle pain. Asking the patient to go down into a squat position can effectively test a very effective test for gamma pain. This

causes a dysaesthetic burning "cramp" in the thigh or calf, along with a strong sensation of "pulling", resembling a muscle cramp after exercise. This rapidly becomes unbearable within seconds to minutes. This pain may represent a hyperpathic response to pressure, and may resemble that felt by healthy people on sitting in one position for a very long period. Often patients report pain when trying to lie down in bed and they wake up feeling "battered".

Another type of muscle pain is that brought on by activity. In health people, only excessive and prolonged exercise such as that in a marathon run brings on what is termed 'lactic acid build-up' pain. In patients with central pain, this type of pain is brought on within a very short period of activity. (Beric has termed this pain "kinesthetic dysesthesia" ([512]). It may be sufficiently debilitating that it effectively reduces a patient's functional ability.

"In the most common situation, if a Central Pain patient attempts to exercise, the tonic soreness in the muscles will be unbearable the next day. The onset of dynamic pain is immediate." ([513])

As we shall see below, muscle cramps are a common part of the arachnoiditis picture. They may well be a feature of centralised pain. Localised cramps may persist almost continually. Exercise heightens gamma pain and is the principle reason why patients with arachnoiditis should not be considered non-compliant or even obstructive when they refuse to exercise.

"The physician should look upon dread of movement by the patient as a measure of the almost overwhelming severity of Central Pain, and not as an indicator of patient weakness." (508)

DYSAESTHESIA

This is bizarre pain that typically cannot be described but is generally burning in nature. It is not felt in normal people and is specifically a feature of incomplete nerve damage; it may be experienced in numb areas, but may extend further towards the centre of the body than the numb area.

Patients may find this pain experienced in virtually numb areas particularly difficult to describe and cope with. The loss of sensation seems to be partial rather than total, and the complication of the bizarre and highly unpleasant dysaesthesia is one of the predominant features of arachnoiditis.

It may sometimes be called deafferentation pain, or causalgia**.** Many patients suffer from burning feet in particular. Dysaesthesia is rather like an "afterburn", resembling the pain of having just touched a hot stove, with a poorly defined 'flare' of pain. Some patients describe a metallic quality to the pain. It may also seem simultaneously burning and freezing.

Tasker described a steady state level of "spontaneous" pain, which may be increased by light touch, clothes rubbing or temperature change. This increase is called "evoked pain" and is worse in areas where sensation is most reduced, nearly always in the extremities. It is an extreme pain, and may last for half an hour or so after the stimulus, although it does reduce by about a quarter once the stimulus is removed. Getting the skin temperature to the most comfortable level can reduce this evoked pain more quickly.

Evoked pain shows what is called “slow summation” i.e. it builds up gradually, with an initial time delay. Long exposure to stimulus (such as contact with bed sheets at night) is especially unpleasant.

HYPERPATHIA

This is increased pain from a stimulus that would be painful to normal people. Unlike dysaesthesia, it tends to be more proximal (nearer the centre of the body).

It also has a delay, but not one of time, rather what is termed “delay with overshoot”, which means that there is a raised threshold for pain, but when that threshold is reached; there is an overshoot of pain, out of proportion with the stimulus.

Visceral hyperpathia can occur. This can affect both bladder and bowels, so that sensation of fullness is delayed and then becomes urgent and is often dysaesthetic i.e. burning (e.g. bladder burning). This may lead to embarrassing accidents!

ALLODYNIA: (“other pain”): this is pain from normally non-painful stimuli or pain outside the area being stimulated (but is not the same as referred pain). It tends to be dysaesthetic.

It is very often triggered by changes in temperature, in which both hot and cold stimuli are perceived as hot, (termed “read only burning”: ROB); light touch such as clothing may cause pain. Pain may be referred from other areas when they are stimulated. Continual or repeated stimulation can cause severe pain that persists after the stimulus is withdrawn.

CP (central pain) sufferers have a narrow window of comfort as regards temperature changes. For this reason, cold draughts may be especially unpleasant, and hydrotherapy pools may be too hot.

LANCINATING (SHOOTING) PAINS

These are usually in areas where there is dysaesthetic burning, but they are very localised. The pain radiates, and may vary from being like an insect bite to an electric shock. The majority of patients have these transient shooting pains.

CIRCULATORY INSUFFICIENCY

This refers to nerve circulation (not blood), and manifests itself as “pins and needles”.

VISCERAL:

Hyperpathia, as mentioned above, may affect the internal organs and may cause simple flatus to be experienced as severe cramping pains.

DISTORTIONS OF BODY SIZE PERCEPTION

In much the same way as your lip can feel odd after a dental anaesthetic, so too can parts of your body, usually those parts most affected by sensory loss and burning.

BIZARRE SENSATIONS

Typically, arachnoiditis patients report a variety of strange sensations affecting various parts of the body. These include feeling as if they are walking on broken glass, water running down the leg, sensation of insects crawling on the skin etc. They tend to be reluctant to report these experiences for fear of being diagnosed with a mental illness.

SENSORY ATAXIA

Sensory loss in the feet leads to trips and falls. Loss of proprioception (sense of where the feet are in relation to the ground) can mean that the patient feels their feet aren't really touching the ground.

AUTONOMIC EFFECTS (see below)

These include: excess sweating, changes of skin colour from white to purple, minor swelling, shininess of skin; also: fluctuating blood pressure (greater than usual response to physical stress such as change in temperature or position e.g. from lying to standing) These effects are exacerbated by cold or emotional upset.

In summary:

Central pain causes burning pain, often with a paradoxical component of cold, and is made worse by light touch or the rubbing of clothing (Bowsher's criteria[514]). It affects large areas of the body, or even its entirety, as it originates centrally rather than in the spinal cord. This may lead to fear that the disease has spread or may cause doctors to dismiss symptoms as psychological.

DISUSE SUPERSENSITIVITY

Structures which are supplied by a nerve, rely on this innervation to maintain function and integrity; loss of the nerve's regulatory ('trophic') effects leads to these structures becoming highly irritable and supersensitive. This phenomenon can affect nerves, muscles, brain cells, sweat glands and the adrenal gland. These structures behave abnormally, 'over-reacting' to many forms of input, not just pain signals.

Breakthrough Pain

Simmonds ([515]) has used a definition of breakthrough pain as:

"The transient exacerbation of pain occurring in a patient with otherwise stable, persistent pain."

She notes that this is a common phenomenon in cancer patients and is "one of the most difficult pain syndromes to treat."

The American Pain Society recently ([516]) defined breakthrough pain as:

"Intermittent exacerbations of pain that can occur spontaneously or in relation to specific activity; pain that increased above the level of pain addressed by the ongoing analgesic; includes incident pain and end-of-dose failure."

It can be caused by somatic, visceral or neuropathic physiology and tends to be related to the same mechanism responsible for the underlying persistent pain.
Breakthrough pain is often paroxysmal, rising to a peak of intensity rapidly, although it can be of more gradual onset. Portenoy and Hagen ([517]) characterised breakthrough pain as rapid in onset (within 3 minutes) and of short duration (median 30 minutes).

Breakthrough pain may be related to movement (*incident pain*) or unrelated (*spontaneous pain*). Incident pain can arise due to volitional movement (such as walking) or nonvolitional movement, such as bowel or bladder distension. Spontaneous pain is not linked to scheduled analgesic dosing, and should not be confused with inadequate analgesic levels which cause an increase in pain as the dose wears off (this is known as 'end-of-dose' failure').
Lancinating pains are a common example of spontaneous pain.

SITES OF PAIN

The areas commonly affected by pain are:
In most cases: lumbar, buttocks, legs (often both), feet, perineum, hip and abdomen.
In some cases: arms and hands, neck, head and face, chest.

In the New Zealand survey: Lower body symptoms: 83% had back pain, 41% buttocks, pelvis, hips, groin (6% in genitalia), 85% legs, knee, ankles, 53% feet and toes.
Upper body symptoms: Arms/shoulder 32%, hands/fingers 12%, neck 30%, head/face 29%, chest 6%.
Generalised pain was reported in 8% of respondents.
Diffuse soft tissue pain was reported by 55% of respondents in the New Zealand Survey, 48% of the global survey (under the criterion fibromyalgic pains) and 41% in Long's study ('diffuse pain- non-radicular').

Musculoskeletal pain: Pain that can be localised to sites of muscle, ligament or bone abnormalities.
Note: Secondary musculoskeletal pain can be present in more or less any area, regardless of the site of the spinal nerve root damage.
These include pain at the site of instrumentation (e.g. Harrington rods, Steffee plates, pedicle screws etc.) and that resulting from the stress and strain placed on remaining joints and ligaments after injury or surgery. Fixation or damage in one or more spinal segments results in greater stress of remaining non-fixed segments.
Compensatory posture changes to protect the painful lumbar area, coupled with loss of paraspinal muscle mass, put much more strain on the upper back, especially at the thoracolumbar junction, which may account for some abdominal pain* and the neck, which may contribute to neck and arm problems.

Disuse, overuse or compensatory use of muscle groups, causes alteration of spine dynamics. There may also be muscle tension due to being in pain, or increased muscle tone (spasticity) caused by nerve damage. Joint pain may be due to similar factors, or may be part of the autoimmune picture (see below).
Temperomandibular joint dysfunction is quite common and could be due to nocturnal bruxism as a result of pain experienced even whilst asleep.
A significant proportion of the musculoskeletal symptoms might be due to myofascial trigger points.

(* This might actually be referred pain.)

Hip or groin pain may be due to sacroiliac joint problems.

Perineal pain may include vulvodynia and proctalgia fugax. (See below)

Abdominal pain: visceral hyperpathia can make abdominal cramps secondary to constipation extremely painful. Quite a few patients complain of a diffuse, dragging abdominal pain, often in a distribution suggestive of thoracolumbar junction stress. This could be due to loss of muscle mass in previous operation sites, usually lumbar.

Chest pain: there are a number of patients who experience either angina type pain (but cardiovascular system checks out normal) or pleuritic type pain that increases on breathing in. The latter could be due to intercostal muscle tenderness.
There may also be chest pain due to oesophageal reflux. This may be accompanied by difficulty swallowing.

Pain in the throat with a feeling like a lump is stuck could be dismissed by doctors as “globus hystericus” but might be due to trigger points in the pterygoid muscle or to anterior osteophytes in the cervical spine.

Pain and swelling in the hands may be diagnosed as carpal tunnel syndrome but could be more related to spinal problems.

Facial pain: Some patients seem to suffer from trigeminal neuralgia and there are a few who have symptoms suggestive of geniculate neuralgia, superior laryngeal neuralgia, glossopharyngeal neuralgia or occipital neuralgia.

Trigeminal neuralgia: affects the face, including the jaw and may radiate round to the ear, and affect the front part of the scalp. Pain is very severe, sharp, shooting, 'like an electric shock'; it is right-sided in 60% of patients and bilateral (both sides) in 3% and is paroxysmal. A period of hyperaesthesia (hypersensitivity to touch) then dull ache may continue after the paroxysm.
Attacks (clusters of paroxysms) may last for days or months. Intervals between attacks may last for weeks or years.
Associated features include: anxiety, poor oral hygiene (reluctance due to extreme discomfort), weights loss due to difficulty in eating and depression.
Precipitation of attacks: stimulus of a trigger point (usually skin / mucosa of the central face). This may be due to light touch, speaking or eating.
Neurological examination is normal; CT and MRI are normal; so diagnosis is on symptoms (history).
“Atypical” trigeminal neuralgia may cause a burning pain deep in the face.

Geniculate neuralgia: causes pain deep within the ear may be described as "an ice pick in the ear". Triggers may include exposure to cold wind, touching the face, chewing, swallowing, talking, and eating ice cream.
Both may result from herpes zoster (shingles)

Odontalgia (tooth pain) is another fairly common phenomenon, and many arachnoiditis patients need to seek frequent dental attention yet no dental source for the pain can be found. (Note that any dental problems which do occur may be related to dry mouth due to medication, which may cause increased tooth decay due to loss of the protective saliva; also osteoporosis may lead to receding gums)
Temperomandibular joint (TMJ) dysfunction is quite common (clicking jaw) and could be due to nocturnal bruxism (teeth grinding) as a result of pain experienced even whilst asleep**.**

HEADACHES IN ARACHNOIDITIS

Headaches are common in arachnoiditis and may arise for a variety of reasons, including muscle tension. In individuals who have a history of iophendylate (Myodil/Pantopaque) myelography, residual dye in the basal cisterns may be the culprit.

Aldrete reported frequent headaches (more than 4 a week) in 80% of his survey cases. 59% of the New Zealand survey respondents reported this problem.

Headache experienced more than 15 days a month falls in the category Chronic Daily Headache, which includes various types of headache.

The International Headache Society, IHS, has categorised chronic daily headaches.
Chronic daily headache is a widespread clinical problem and accounts for almost 40% of patients seen in specialty headache clinics. Although these tended to be regarded as chronic tension-type headaches, from clinical studies, however, it is clear that these are different types of headaches, of which, tension-type headaches in fact form only a minority. Headaches may be classified as follows:

I. Chronic tension-type headache - form only 10%
II. Migraine chronic tension-type headache complex
    A. Transformed from episodic migraine
    B. Transformed from episodic tension-type headache that are either drug-induced or non-drug related.
III. Chronic new persistent daily headache
IV. Post-traumatic headache

Some of these headaches may be due to excessive use of symptomatic medication, including the category of 'transformed migraine' in which people with migraine headache begin to use excessive amounts of over-the-counter medication. They develop a tolerance to medication over a period of time, therefore needing more

tablets to control the headache. They then develop withdrawal symptoms and get daily headache. Medications of this type include non-steroidals, aspirin, and other over-the-counter analgesics.

ACUTE DRUG-INDUCED HEADACHE

1. Acute drug-induced headache can be caused by many drugs including:
    - Nitroglycerin, antihypertensives (beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, and methyldopa), dipyridamole, hydralazine, sildenafinil Histamine receptor antagonists (such as cimetidine and ranitidine) NSAIDs especially indomethacin Cyclosporine, amphotericin, grise ofulvin, tetracycline, and sulfonamides.
2. Drug-induced aseptic meningitis (see also above)

a. Numerous causes

1. NSAIDs
2. Antibiotics (trimethoprim/sulfamethoxazole, sulfasalazine, cephalosporins, ciprofloxacin, isoniazide, and penicillin
3. Intrathecal drugs and diagnostics (antineoplastics such as methotrexate and cytarabine; gentamicin; corticosteroids; spinal anesthesia; baclofen; repeated iophendylate for myelography; and radiolabelled albumin)
4. Intraventricular chemotherapy
5. Intravenous immunoglobulin
6. Vaccines (polio; measles, mumps, and rubella; and hepatitis B)
7. Other drugs such as carbamazepine, muromonab CD-3, and ranitidine

Note that the clinical presentation is the same as that of viral meningitis and CSF findings are similar to viral meningitis except for neutrophil predominance in most cases, except Intravenous immunoglobulin where there are eosinophils in the CSF.

Headaches in arachnoiditis patients may be:

(i) **Tension:** This type tends to be multifactorial. Sustained contraction of pericranial muscle s (muscle contraction headache) is a common feature, although there is no direct correlation between muscle contraction, tenderness, and the presence of headache (migraine sufferers can experience the same or greater muscle contraction). The tension headache presents often on both sides and may be felt as a tight band across the forehead, and is not aggravated by walking stairs or similar routine physical activity. It may be referred from upper cervical structures (joints, ligaments, and muscles) and could be due to abnormal neuronal sensitivity and pain facilitation. Central sensitisation due to prolonged pain input from the periphery (e.g. legs in arachnoiditis) can affect the trigeminal nucleus caudalis neurons. Physical or psychological stress, lack of sleep, anxiety and depression can also have this effect. Tension-type headache in migraineurs may be different than in non-migraineurs in that it may occur due to the typical migraine triggers and light or noise sensitivity often accompany the headache.

(ii) **Migraine:** possibly due to myofascial trigger points; including vestibular migraines which present as vertigo with or without headache (see below); **Migraine** type headaches often present with auras. It should be noted that there is an association between photoaversion and anticonvulsant treatment, particularly phenytoin and carbamazepine. ([518]) Migraine headaches often involve sensitivity to light and/or noise, and may be accompanied by nausea.

(iii) **Neuralgia:** neuritic pains tend to be brief but severe: stabbing, lancinating pains; (see under facial pain)

(iv) **Cervicogenic headache:** Headache arising from the neck: from structures such as joints, ligaments, muscles and cervical discs, all of which have complex nerve endings.

It is typically dull or aching in the occipital (back of the head), temporal (temples) frontal (forehead) or orbital (around the eyes) regions or any combination of these areas; one sided or both sides

There may well be some indication of neck problems such as neck pain, localised neck tenderness, reduced neck movement, aggravation of the headache by neck movement or a history of neck trauma.

In 1987, Fredriksen, Hovdal, and Sjaastad ([519]), at Trondheim University Hospital in Norway, looked at the clinical manifestations of this headache in 11 typical cases. 6 of the 11 recalled a previous head or neck injury and in 4 the headache had appeared within a month of the trauma. The typical headache attacks were reported to be of 1-3 days duration separated by intervals of 1-4 weeks. The pain was unilateral, strongest in the orbit or temple but also present in the upper posterior neck, steady in most patients, throbbing at times in some, and often accompanied by nausea/vomiting and light and/or noise sensitivity. Attacks were often precipitated by such head movements as "washing the ceiling," "polishing the floor" or "turning the head towards someone during conversation." Physical findings were unremarkable, except that in all except one patient, pain, sometimes prolonged, could be induced by firm manual pressure on the neck. The authors acknowledged that cervicogenic headache could "easily pass for migraine."

In 1998, Sjaastad, Fredriksen, and Pfaffenrath ([520]) published updated diagnostic criteria on behalf of the Cervicogenic Headache International Study Group:

I. Symptoms and signs of neck involvement:

The presence of Point A by itself signifies neck involvement, but points B and C alone do not. However, B and C together provisionally signify neck involvement.

A. Precipitation of head pain similar to the patient's usual pain:
    1. By neck movement and/or sustained awkward head positioning, and/or
    2. By external pressure over the upper cervical or occipital region on the symptomatic side
B. Restriction of the range of motion in the neck
C. Ipsilateral neck, shoulder, or arm pain of a rather vague non-radicular nature or, occasionally, arm pain of a radicular nature
D. II. Confirmatory evidence by diagnostic anesthetic blocks
E. III. Unilaterality of head pain without sideshift

(v) **Rebound** headache due to regular analgesic use, particularly opiates. This type of headache should be suspected if:

- Medications seem to be less effective
- Taking more medication (higher dose or more often), but getting less relief
- Headache is worse 3-4 hours after taking medication
- Preventive medications (for migraines) are not working as well as before
- Need to take medication to avoid severe pain or incapacitation

Dr Timothy Steiner, reader at Imperial College School of Medicine and honorary consultant at Charing Cross Hospital and The Princess Margaret Migraine Clinic, ([521]) suggests that 4% of the population suffer from chronic daily headache, and that "analgesic rebound headache" or "drug-abuse headache" is one cause of this problem. He prefers to use the term "medication misuse headache (MMH)", about which he writes: "This evolution can occur over as little as four weeks or much longer, depending to a large extent on the medication used, although this is not the sole factor... A key factor is that many MMH sufferers use medication pre-emptively, in anticipation of headache and before its onset."

The MMH headache tends to be oppressive and is often present on waking up in the morning, and increases during and after physical exertion. Nausea such as experienced in migraines is infrequent and less pronounced. Once well established, MMH may involve a headache that persists all day, fluctuating with (and despite) medication use, which tends to be repeated every few hours. Migraine prophylaxis is ineffective, as is the use of amitriptyline.

Combination analgesics have been suspected of being particularly related to development of MMH, but Dr. Steiner suggests that there is no "evidence that they promote the condition more readily than simple analgesics alone." Prophylactic (preventive) drugs for migraines such as ergotamine and triptans are however known causes of MMH. Dr. Steiner also points out a possible link with NSAID or opioid medication, as gastrointestinal symptoms have been reported in nearly 40 per cent of patients with MMH. (NSAIDs can cause upper gastrointestinal distress and opioids are associated with constipation).

(vi) Frequent sinusitis may cause **sinus related headache** with sensation of fullness around the face (these headaches tend to be worse on bending forward, also first thing in the morning and on exercising.) Headache is one of the key symptoms in acute or chronic sinusitis. In addition to a headache, sinusitis patients may experience: pain and pressure around the eyes, across the cheeks and the forehead, an achy feeling in the upper teeth, fever and chills, facial swelling, nasal stuffiness and possibly a yellow or green discharge.

(viii)**Myodil-related headaches**

Wicke et al (in Germany) ([522]), Mamaurian and Briggs ([523]) and Hackney et al. ([524]), described **retained residuals**, whether intracranial or intraspinal, as **'common'**.

In 1982, Avrahami and Cohen ([525]) published an article in German concerning post-myelography headaches persisting for more than 6 months. The authors suggested that these were the result of residual Pantopaque causing blood vessel irritation.
In May, 1983: Junck and Marshall ([526]) stated: "The most important adverse effects observed with myelographic agents include **acute and chronic meningeal reactions with iophendylate**, and seizures and transient encephalopathy with Metrizamide."

(viii) **Low blood sugar:** chronic stress and constant pain may cause increases or fluctuations in circulating levels in hormones such as adrenaline, cortisol and insulin. The latter may result in fluctuating blood sugar levels. Low levels may induce headache associated with anxiety, sweating, pallor and sometimes aggression or agitation or feeling faint. Eating a high sugar meal may result in onset of symptoms 3-4 hours later as the body may overcompensate for the rapid increase in blood sugar by releasing high levels of insulin which then cause what is termed "rebound hypoglycaemia": a low blood sugar. The shaky feeling and other symptoms would resolve quickly on eating food, especially if it is high in sugar.
(ix) Caffeine-related: a study of short-term caffeine withdrawal looked at adults with a low-moderate daily caffeine intake of an equivalent of about 2.5 cups of coffee (mean of 235 mg) per day
Upon withdrawal of caffeine, 50% had a headache by the second day, with other symptoms such as nausea, depression, and flu-like symptoms. In patients with frequent headaches, it can be helpful to obtain a history of caffeine use in over the counter and prescription medications as well as beverages and ice cream. Some examples of caffeine content include: 12 ounces of Coca-Cola contains 45 mg
8 ounces of brewed coffee contains 135 mg.

Less commonly:
Occipital headaches: radiating from the back of the head, forwards to behind the eyes, with possible feeling of pressure around the temple. : Onset of these is usually after exertion, valsalva manoeuvre (e.g. opening the bowels) or bending forward. These seem similar to headaches due to raised intracranial pressure. One can note a similarity with Chiari-1 malformation.
Neurosurgeon Michael Rosner in USA suggests that Chiari malformation may be seen in Chronic Fatigue Immune Deficiency Syndrome (CFIDS) and Fibromyalgia (FMS), both of which are quite often diagnosed in arachnoiditis patients. A recent study in USA ([527]) has linked Chiari with FMS: of 364 patients with Chiari, nearly 60% had a prior diagnosis of Fibromyalgia, 12% of CFS, 31% migraine/sinus headache, 9% MS and 63% psychiatric/malingering.

Features of Chiari include: occipital headache* radiating behind eyes (exacerbated by exertion, especially leaning the head backward or coughing); disordered eye movements, vision changes; dizziness, autonomic symptoms (orthostatic hypotension, NMH); muscle weakness; unsteady gait; cold, numbness and paraesthesiae in extremities; chronic fatigue; tinnitus; sleep apnoea; hearing loss; Irritable Bowel Syndrome (IBS); frequent urination; difficulty swallowing. As we have seen from the survey results, many of these symptoms are seen in arachnoiditis. (* Headache occurs in about 50% of Chiari cases and the brief type

tend to be caused by transient herniation of the base of the brain, part of the brain stem called the tonsils down through the hole at the base of the skull into the spinal canal)
Sansur et al. ([528]) recently looked at the pathophysiology of headache associated with Chiari 1 malformation. 26 patients had Chiari 1 plus syringomyelia, 4 had only Chiari. They found that headache linked to coughing in patients with Chiari I malformation is associated with sudden increased intrathecal pressure caused by obstruction to the free flow of CSF in the subarachnoid space

A further possibility is intermittent raised intracranial pressure similar to that seen in a condition called pseudotumour cerebri or benign intracranial hypertension (BIH). In this condition, there may be severe, frequent headaches that are worst in the morning (and may indeed waken the patient), visual disturbances (transient blurring or loss of part of the visual field) and sometimes a pulsatile tinnitus (pulsing sound in the ears). This has not been proven as such in arachnoiditis, but there is a known association between arachnoiditis and a condition called hydrocephalus which leads to enlarged ventricles in the brain due to raised pressure of the CSF; another similar condition affects the spinal part of the CSF: syringomyelia. It may well be that the scar tissue of arachnoiditis impairs normal CSF circulation and this affects the pressure gradient in what is a closed system.

Chest pain

There have been occasional cases of angina-type chest pain in arachnoiditis. It is interesting to note that Kumar et al. ([529]) reported a case of intradural arachnoid cyst at T3-5, which presented with episodes of cardiac type chest pain although all cardiac investigations proved normal. The authors suggested that the pain arose due to aberrant stimulation of the sympathetic outflow tracts T3-4. The upper thoracic spinal nerves communicate with the sympathetic chain ganglia; the medial branches of the upper five ganglions send fibres to the cardiac plexus. They proposed that the aberrant stimulation was brought on by changes in osmotic pressure within the arachnoid cyst as a result of venous engorgement arising during physical exertion.
A similar effect might occur with arachnoid adhesions at this level.

SPECIFIC TYPES OF PAIN

'IDIOPATHIC' PELVIC PAIN

Possible overlooked organic neurological causes:
Lumbosacral plexopathy including Cauda Equina Syndrome
Pudendal neuralgia
Perineal neuralgia

Pelvic pain may arise through local trauma as well as a number of medical conditions such as iliac artery aneurysm. However, in situations where there has been recent surgery, one must bear in mind adverse effects from (a) epidural/spinal anaesthesia and (b) positioning during the procedure. (lithotomy position, for example, may be linked with a higher incidence of pooling of anaesthetic in the cauda equina region). One must also factor in the effect of urinary catheterisation should this have been necessary.
Pain/paraesthesia in the perineal area, plus disturbances in bladder/bowel/sexual function would suggest a *cauda equina* lesion. Whilst it is a well-recognised (though sometimes belatedly so) acute condition, there is also a chronic form.

Cauda Equina Syndrome

Severe pain in radicular pattern: back, buttocks, perineum, genitalia, thighs, legs. Note that neuropathic pain is generally persistent, burning in nature and may also be briefly stabbing/ lancinating and/or electric shock sensation; this type of pain is usually worse at night and, definitively, may be present in areas which have reduced sensation (including numb areas)

- Loss of sensation: often tingling or numbness in the saddle area.
- Weakness: in legs, often asymmetric
- Bladder/bowel/sexual dysfunction: incontinence/ retention of urine; incontinence of faeces; impotence/loss of ejaculation or orgasm
- Loss of reflexes: knee/ankle reflexes may be diminished, as may anal and bulbocavernosus.

Foot pain:

The majority of arachnoiditis patients experience burning in the feet, often to the extent of being unable to tolerate footwear of any kind. In addition, many describe a sensation of “walking on broken glass”.
Aldrete has described cases of plantar (sole) neuroma, which may cause pain on walking. In his survey, 6.7% of his respondents had this condition. He attributed this to repetitive irritation of the metatarsal nerves due to abnormal gait and foot posture in arachnoiditis patients. Symptoms of plantar (Morton’s) neuroma include: agonising pain in the sole after walking/standing in closed shoes for a period of time; localised pain from which relief is gained by stopping, sitting down and removing footwear and resting or massaging the foot. More diffuse pain may well be from a different source. Typical descriptions are “like walking on a pebble” or “having a hot poker thrust between the toes”. Between attacks, patients may be able to walk without limping.
Other causes of foot pain include plantar fasciitis (heel pain, with inflammation of the thick band of tissue in the sole of the foot); heel pain due to nerve entrapment, heel spur or as part of inflammatory conditions such as rheumatoid arthritis or gout. Metatarsalgia is a condition in which pain is felt directly under the affected bone (the long bones running towards the toes).

Other neurological symptoms

Sensory

Aldrete attributes some of the transient sensory phenomena to ectopically generated nerve impulses, which implies a sensory equivalent to the motor effects.

- **Tingling and numbness;** the tingling may be intense enough to be painful. Numbness is typically incomplete and pain may be felt in the affected area. In the New Zealand survey, 71%, Global survey 86% and Aldrete's survey 81% of respondents reported this symptom. Loss of sensation in the feet requires vigilance for damage (cuts, abrasion, infection) much as in cases of other causes of peripheral neuropathy.
- **Loss of proprioception** (sense of limb position up or down in relation to ground) causing tripping and falls. Impaired proprioception, especially when combined with a slight or moderate motor weakness, may cause the feeling that the legs are going to collapse. In addition, there may be a sensory ataxia. Together these problems can cause falls and thus fear of future falls, which can lead to a patient becoming less and less mobile, thereby worsening the problem through muscle wasting due to disuse.
- **Tinnitus:** buzzing/ringing/whistling/hissing/pulsing in the ears with possible heightened sensitivity to external sounds (hyperacusis) (in about 60% of those with tinnitus). May be a feature of the overall CNS hypersensitivity; less than 5% of cases have an ear-related problem. Causes that need to be excluded include Meniere's disease, raised blood pressure, overactive thyroid (note: this can occur in people who have had a myelogram), raised intracranial pressure and salicylate (aspirin) use; note also that caffeine, alcohol and nicotine are associated with tinnitus.
- In the Global survey 44% of respondents had **dizziness/vertigo**.

Dizziness can encompass a range of sensations, but usually refers to:

Light-headedness

Feeling faint/a loss of balance/ unsteady

Giddiness

Vertigo: vertigo of cervical origin has been described in one paper ([530]), with features of ataxia (unsteady gait). Vertigo refers to a sensation of spinning or falling. Sitting up or moving around may make it worse, and it may be bad enough to cause sickness.

Common causes of dizziness/vertigo or unsteadiness related to arachnoiditis include:

- Medication: including salicylates (aspirin), caffeine, alcohol, anti-seizure drugs (given for pain) sedatives etc.
- Vestibular migraine
- Low blood pressure, abnormal heart rhythm: may cause faintness: a drop in blood pressure on standing (orthostatic hypotension) is a relatively common problem (contributed to by autonomic neuropathy)
- Autonomic neuropathy

- Metabolic disturbance: including low glucose, hypothyroidism
- Allergy

NOTE: If you have developed sudden weakness or tingling/numbness down one side of your body, in association with dizziness, you should seek immediate medical attention to exclude a stroke.

Eye problems: In the 1999 survey, 45% of respondents said they had some sort of visual problems. Further investigation revealed that common problems included:

Photoaversion: intolerance of bright light: a very common problem, most often after myelograms or epidural injections; it may be due to hypersensitivity of the nervous system. Specific ocular (eye) causes include: conjunctivitis, uveitis, and dry eye.

Dry eyes: A gritty feeling or just sore eyes seems to be a common problem with arachnoiditis. In a few people, a condition called Sjogren's syndrome may be diagnosed: this involves dry eyes and mouth and joint pains. Dry eye syndrome is usually due to reduced aqueous tear production (keratoconjunctivitis sicca), reduced quality of the tear film, disorder of the corneal surface or a lid dysfunction. Other disorders that can cause dry eyes include rheumatoid arthritis and SLE (lupus), connective tissue disorders (sarcoidosis, amyloidosis) and Stevens-Johnson syndrome. Drugs that may cause reduced tear flow include: diuretics, antihistamines, tricyclic antidepressants (e.g. amitriptyline), oral contraceptive pill, atropine derivatives, and beta-blockers (this list is not comprehensive). Symptoms include transient blurred vision and aversion to bright lights.

Blurred vision: this is probably most commonly a result of medication such as morphine and related drugs. Other causes require full ophthalmic assessment. Anticholinergic drugs such as the antidepressant amitriptyline, may affect the ability to focus, as may morphine and related drugs.

Pain around the eye: these can be sharp, lightning pains, which can feel as if they go right through the eye. They can be related to neuralgia

Eye symptoms in migraine: these may include seeing an 'aura' before onset of the headache.

Conjunctivitis: infective inflammation of the conjunctiva; chronic illness may generally debilitate and therefore predispose to infection.

Less commonly:

Uveitis: inflammation of the eye: if the front of the eye is involved, the eye will be red, and there will be light sensitivity, and some reduction in vision; often it occurs in one eye and there is rapid onset of symptoms; if the back of the eye is affected, these symptoms may not occur, except for reduced vision which can range from mild to severe; both eyes may be affected.

Floaters: these are tiny clumps of cells in the fluid behind the pupil (vitreous humour) at the back of the eye, which appear, however, to 'float' in front of the eye. They cast shadows on the retina, the nerve layer at the back of the eye. Floaters may appear as a variety of shapes including dots, lines, cobwebs, circles, clouds. Generally, they are harmless, but can be a nuisance if they interfere with activities such as reading.

Occasionally, new floaters can arise due to *posterior vitreous detachment*, which is when the vitreous gel shrinks away from the retina. This is more common in older middle-aged people who are nearsighted, have undergone cataract surgery, have had previous laser treatment, have had inflammation in the eye or have had head trauma.

Horner's syndrome: often an acute condition which can occur after epidural injection: all the symptoms are on one side of the face. They comprise: drooping eyelid, skin feels warm and dry (no sweating) and pupil constricted. Horner's may also occur if spinal nerve roots in the neck are damaged.

Raeder's syndrome: a combination of pain, drooping eyelid and constricted pupil; there may be a preceding history of episodic pain in or around the eye and cluster headaches. This is a benign condition that may arise during a cluster of headaches and resolving spontaneously once the headaches have ceased.

Adie's Pupil: a 'tonic' (poorly responsive) dilated pupil, which may be associated with a generalised *dysautonomia*, that is, abnormal autonomic functioning that is occasionally seen in patients with arachnoiditis.

Thyroid eye disease: some arachnoiditis patients who have a history of a myelogram (oil or water-based contrast agent) may develop thyroid disorders. This could be related to the iodine content of the myelogram dye. Hyperthyroid disease may present with eye problems: this is termed *Grave's disease*. Common symptoms include: eyelid retraction, irritation in the eye, watery eyes (or dry eyes if the eyelid retracts considerably), redness, double vision, pain and reduction in vision. The eyes may appear to 'bulge' because the fat and muscles around the eye may be infiltrated with antibodies; this may put pressure on the optic nerve, and cause problems with vision. There may be difficulty in moving the gaze around, because the muscles around the eye are not working properly.

Rare problems that may occur:

Optochiasmic arachnoiditis: a particular subtype of arachnoiditis; it may occur after eye surgery. (See above)

Raised intracranial pressure shows up in eye examination as swollen optic disc (where the optic nerve leaves the back of the eye): known as papilloedema. This can result from hydrocephalus (a complication of arachnoiditis) or pseudotumour cerebri (Benign intracranial hypertension).

Some arachnoiditis patients have been told that their eye problems resemble those seen in **Multiple sclerosis**.

ITCHING (PRURITUS)

In Aldrete's survey, he found that 5% of his respondents suffered from pruritus. Most itching is worst at night, and may thus disturb sleep.

Certain autoimmune and neurological disorders may cause this type of problem. Drug treatment may also be the cause. Neurogenic pruritus has been noted in conditions such as Multiple Sclerosis and stroke. It has also been seen in patients with Systemic Lupus Erythematosus. (SLE).

Drug-induced itching: commonly seen with: Opiates, CNS stimulants/depressants. Allergies may also be implicated: sensitivity to a variety of drugs seems to occur in some arachnoiditis patients

MOTOR PROBLEMS

Motor nerve damage may cause **loss of muscle strength**, especially in the lower back and legs, in some patients. In most cases with weakness, it is mild, but it may progress sufficiently in some patients to necessitate use of walking aids or a wheelchair. Long found that 84% of his survey patients walked alone, whilst 15% used aids and 1.2% were wheelchair bound. Patients with thoracic cord involvement developed progressive paraplegia and 2 with cervical arachnoiditis became quadriplegic.
Aldrete reported abnormalities of gait in 48% of his patients.

A COFWA (online USA-based support group) member, David Gaub, ran a small survey in late 1998, to assess the impact of arachnoiditis on walking. 49 COFWA members took part, the majority of whom had undergone multiple spinal insults. On average, they had begun to experience sustained walking difficulties 12 years after their initial back problems. Mr. Gaub felt that the most significant finding of the survey was that most respondents developed walking difficulties after an incident such as a fall, auto accident, further surgery or meningitis. In some cases, the incidents were relatively minor and the resultant loss of function could not be directly attributed to damage from the incident itself. However, 31 of them described a rapid deterioration since the incident. It may be that decline within a couple of months relates to a threshold number of affected motor nerve roots being reached and breached, so that the muscles supplied by those atrophying nerve roots will start to waste and lose strength progressively. It may also be simply that additional nerve root damage is sufficient to affect enough different muscle groups for the overall functional deficit to be clinically significant whereas previously it had remained occult.
38 of the respondents reported using an assistive device such as a cane or a walker, 10 used a motorised scooter or a wheelchair most of the time. They noted problems with fatigue, relationship issues and limits of socialisation. Depression is common, the effect on morale being understandably severe bearing in mind the loss of physical activities enjoyed previously, and the increasing isolation experienced.

Weakness:

	New Zealand	Global	Long
Weakness	**67 %**	**82 %**	**74 %**

was reported in Aldrete's study as paraplegia in 3 cases (1.8%).
In the global survey, 68% of respondents had reduced mobility (house/chair/bed bound).

Also, many patients report that their muscles **fatigue** more quickly than before. There may be compensatory overuse of some muscle groups to allow the patient to walk, but this leads to the muscle fatiguing more rapidly than normal. This is similar to the picture seen in Post Polio Syndrome (PPS).

Balance problems: may be due to a combination of sensory impairment (loss of proprioception and other sensory modalities) and motor deficit. In the Global survey, 70% of respondents reported this problem (49% in New Zealand survey).

Increase in muscle tone is quite a common feature and makes the legs stiff, which may have an effect on mobility. 73% of the New Zealand survey respondents and 79% of the Global Survey reported stiffness. Aldrete recorded hyperreflexia in one leg in 4.3% of his patients, and hyporeflexia in one leg in 60% (both legs 36%). Moreover, Long noted that chronic muscle contractions (usually secondary to surgery) were recorded in 94% of his survey patients.

Spasticity is increased resistance to passive limb movement, also called hypertonia. This can be caused by upper motor neurone damage or by biomechanical changes in muscles affected by abnormal spinal dynamics. The neurogenic component of spasticity can cause muscles to be held in a contracted state over prolonged periods. This in turn can lead to shortening of the soft tissues and further biomechanical changes within the affected muscle. Left untreated, severe cases can involve abnormal limb posture, which prevents muscle stretching and perpetuates further deformity.
Spasticity can cause harmful effects:

- Muscle spasms are associated with pain and difficulty in sitting and maintaining posture
- Abnormal trunk and limb posture can be associated with contractures and pressure sores
- Loss of function leads to reduced mobility and difficulty with self-care and hygiene and later osteoporosis
- Fatigue can impact on mood and pain levels
- Secondary effects include difficulty with sexual intercourse, poor sleep patterns and depression

Spasticity is not always harmful: patients who have combinations of muscle weakness and spasticity may rely on the increased tone to maintain the ability to stand or walk.

Spasticity is measured using the Ashworth scale:
Grade 0 is no increase in tone
Grade 1 is a slight increase giving a 'catch and release' effect, or minimal increase of resistance at the end-range of movement when the limb is flexed or extended.
Grade 1+ is slight increase in tone giving a catch followed by minimal resistance throughout the remaining range of movement

Grade 2 is more marked increase in tone through most of the range of movement, although affected parts still move easily

Grade 3 is considerable increase in tone such that passive movement is difficult and the joint movement of range is limited.

Grade 4 involves affected parts being rigid either in flexion or extension.

Muscle spasms and cramps may be violent and painful, particularly at night and may persist for several hours. **Muscle twitches** (fasciculations) are usually painless and transient. In the Global survey, 81% of respondents experienced this type of problem, 89% of the New Zealand respondents and 91% of those in Long's survey. Aldrete found 64% of his survey cases suffered from muscle spasm.

Note: fasciculations and cramps may be seen in Hyperthyroidism (history of myelogram dye is a risk factor). Cramps and stiffness with muscle pain may be features of hypothyroidism.

Myoclonus: a brief, sudden, shock-like muscle contraction, mediated by an electrical nerve discharge originating in the central nervous system. Secondary Myoclonus is seen in conditions in which there is central nervous system damage, which, in arachnoiditis, is likely to be related to the spinal cord, so would be termed *spinal myoclonus* (other types include *peripheral myoclonus* from an electrical impulse in a peripheral nerve). *Myoclonic jerks* can be extremely debilitating as they interrupt normal posture and movement. The muscle spasms may be uncontrollable and may be both forceful and painful. They may be triggered by movement (*'action' myoclonus)*, so may not be present when at rest or asleep. There may also be sudden reduction in muscle contraction that prevents normal movement: this is termed *negative myoclonus (asterixis).*

Note: *Drug-induced myoclonus:* about 80 causal agents (toxins and drugs) including:

- Tricyclic antidepressants e.g. amitriptyline
- SSRIs e.g. Prozac
- Penicillin
- Morphine
- Hydromorphone (an opiate related to morphine)
- Phenytoin
- Midazolam
- Pseudoephedrine (available in some over-the-counter common cold preparations)

Cramps: Sudden involuntary painful muscle contractions. Most often, cramps occur following voluntary contractions (e.g. after exercise), and occasionally during rest or sleep. They usually involve single muscles rather than groups. Cramps may be seen in healthy people, usually in the calf muscle. In patients with neurological disorders, cramps may occur in other muscles and may be associated with partial denervation or other neuromuscular conditions, as well as in hypothyroidism (under active thyroid gland) electrolyte

disturbances (metabolic abnormalities affecting salts in the blood). Nocturnal leg cramps are a common problem in arachnoiditis. (See also above under central pain).

Muscle spasms and cramps similar to the Painful tonic spasms (PTS) seen in MS may be violent and painful. Muscle fasciculations are usually painless and transient.

Muscle shortening is an important factor in neuropathic pain, and is caused by muscle spasm and contracture. Muscle shortening produces pain by pulling on tendons, straining them as well as distressing joints they move. Muscle shortening also increases joint 'wear and tear' and contributes to degenerative changes such as tendonitis, and osteoarthritis.

A number of patients complain of symptoms suggestive of **Restless Legs Syndrome**, with nocturnal unpleasant sensations in the legs, accompanied by motor restlessness.
Diagnostic criteria as defined by the Restless Legs Study Group are:

- Desire to move the extremities, often associated with paraesthesias/dysaesthesias*
- Motor restlessness
- Worsening of symptoms at rest with at least some relief by activity
- Worsening of symptoms in the evening or at night

RLS may be primary or secondary to diseases or drugs.
Systemic diseases associated with RLS include: diabetes, rheumatoid arthritis, spinal cord and cauda equina damage, radiculopathies (nerve root damage: as in arachnoiditis), thoracic spinal lesions, complete spinal cord injury and neuropathy.

Medications that may exacerbate or trigger RLS include: Paroxetine (an antidepressant), Mianserin, Phenytoin, caffeine, alcohol and nicotine.

Other problems with muscle spasms include: Less commonly there may be trouble swallowing, sometimes due to oesophageal muscle spasms.

Foot drop:
In some arachnoiditis patients who have scarring at L4/5 or L5/S1 (the spinal level at which the innervation for the common peroneal nerve arises) the muscles in the top part of the ankle become too weak to hold the foot at a 90 degree angle which means that as the foot is lifted, it drops down and tends to drag along the floor, which can cause tripping and falling, especially on uneven ground. Sensory loss may make this problem more troublesome. Patients with this problem may try to overcome it by walking with the affected leg swung out with the knee straight and the weight on the other leg, leaning away from the

affected side in order to swing the foot off the ground. This can cause postural problems and put strain on the spine and legs. Commonly, this can lead to sore, swollen knees.

Risk factors for falls:

- Muscle weakness
- Sensory loss
- Poor balance
- Impaired vision: including wrong prescription glasses!
- Low bone density
- Medication
- Stiff joints
- Sensory ataxia

Obviously, many of these factors are pertinent in arachnoiditis patients.

ARACHNOIDITIS, CHRONIC FATIGUE SYNDROME AND FIBROMYALGIA

Some arachnoiditis patients are given the "catch-all" diagnosis of chronic fatigue syndrome (CFS/ME) or fibromyalgia (FMS). From the survey results and other anecdotal accounts, it seems more likely that these non-specific conditions are actually part of the arachnoiditis syndrome.

Goldstein ([531]) has described CFS as a limbic encephalopathy. In his paper, he writes at length about the "associated illnesses" such as fibromyalgia and carpal tunnel syndrome (CTS). He attributes many of the widespread symptoms to trigger points, which are involved with problems such as Temperomandibular Pain and Dysfunction Syndrome (TMPDS). Many of the symptoms he describes correlate closely with those experienced by arachnoiditis patients. He also discusses allergic rhinitis and intolerance of odours, which brings in a similarity with MCS.

Fibromyalgia (FMS) is defined as the presence of both chronic widespread pain and the finding of 11/18 tender points on examination, although only about 20% of FMS patients have this combination (these are most likely to be female). Clauw and Crofford, in their recent paper on fibromyalgia, ([532]) note:

"There is no clear diagnosis for the other 80% of individuals with less than 11/18 tender points, but it is likely that these persons, like FMS patients, also have pain that is 'central' (i.e. not due to inflammation or damage of structures) rather than peripheral in nature."

In an earlier paper ([533]), Crofford et al. noted that patients with FMS exhibit neurohormonal perturbations and disturbed autonomic activity. In 2002, Crofford published a paper ([534]) on the hypothalamic-pituitary-adrenal axis abnormalities, noting that there is "evidence of HPA axis involvement in acute and chronic pain" but that " it is unclear if the observed HPA axis abnormalities reflect pre-existing vulnerability to the FM spectrum of disease, or whether chronic somatic symptoms alter HPA activity."

A recent study in the University of Florida ([535]) has found that FMS patients suffer from severe pain in response to repeated non-painful stimuli such as pressure on the skin. This is very reminiscent of the pain experienced by arachnoiditis patients. Researchers have hypothesised that this problem in FMS occurs after an injury to the central nervous system, which, of course, is precisely the event in arachnoiditis. Recent research ([536]) suggests a link between Chiari malformation and/or cervical stenosis and Fibromyalgia. Many of the symptoms of Chiari or cord compression in the cervical region are also seen in arachnoiditis patients.

FMS/MPS COMPLEX:

This is a 'double whammy': MPS is a pain condition and FMS is a pain amplification condition: it is synergistic: the whole is greater than the sum of its parts. **Myofascial pain syndrome (MPS):**
This condition causes muscular pain that can be relatively widespread. Pain is caused by nodules (knots) causing areas of irritation in the muscle or fascia associated with the muscle (myofascia is a thin, virtually translucent film wrapped around muscle); these are known as trigger points (TrP), which are areas of irritation within extremely tight bands of muscle and or fascia.

Autonomic manifestations of myofascial pain:

* **Vasomotor:** blood vessel constriction: causing an area that is cold to the touch
* **Pilomotor:** goose bumps in the affected area

Matchstick test: firm indentations made with the blank end of a matchstick in the affected area will take longer to disappear than in unaffected areas. (Source: Myofascial Information Network, Washington, USA)

Autonomic nervous system effects

WHY THE SYMPATHETIC IS OVERACTIVE IN ARACHNOIDITIS:

The central nervous system is damaged in arachnoiditis. It is therefore unsurprising that it may not function normally.

Some possible factors might be:

- Abnormal feedback from damaged nerves
- Thalamic effects: pain, stress
- Limbic system: emotional input?
- Sympathetic chain: direct damage?
- Spinal cord injury>> autonomic dysfunction
- Cervical pathology >> autonomic dysreflexia
- Thyroid abnormalities

- Effects of medication?
- Disturbance of hypothalamic-pituitary axis (seen in some fibromyalgia patients)

Constant pain is a continual stressor, resulting in adrenal over activity and subsequent exhaustion. (Sudden onset fatigue may be associated.)

CLINICAL EFFECTS OF SYMPATHETIC NERVOUS SYSTEM OVERACTIVITY

The 5 commonest problems are:

- Sympathetically-maintained pain
- Excessive sweating (diaphoresis)
- Abnormal bladder function
- Raynaud's phenomenon
- Panic attacks

A common component of the arachnoiditis syndrome is the effect on the **autonomic nervous system**. (Responsible for regulating involuntary processes such as blood pressure and temperature, bladder and bowel function etc.) Disturbance of this system occurs because the nerves involved run along the spinal cord in the "sympathetic and parasympathetic chains" (thoraco-lumbar and cranio-sacral respectively) and also because of the effects of unrelieved pain on stress hormones.

Bowsher's paper ([537]) on central pain describes how most patients with central pain develop "autonomic instability", by which he meant an increase of pain under physical and emotional stress, with cutaneous blood flow and sweating also being affected.

Ziegler et al ([538]) describe how systemic diseases such as diabetes can cause peripheral sympathetic neuropathy, giving rise to postural hypotension, heat intolerance, etc. They also maintain that patients with diseases of the sympathetic nervous system demonstrate marked abnormal stress responses to minor stresses such as change of posture or ambient temperature.

Blood pressure disturbance (high, low or fluctuating); this may cause dizziness, syncope, or headaches. Orthostatic (postural) hypotension may occur. Mathias ([539]) describes how in chronic autonomic dysfunction, pressor stimuli such as mental arithmetic, isometric exercise and cold, do not result in the normal increase in blood pressure. Also, stimuli such as food ingestion, which would normally activate the sympathetic system to maintain blood pressure, tend to actually cause marked hypotension.

Khurana discussed cases with chronic cervical myelopathy who responded to orthostatic challenge with hypotension, followed by hyperhidrosis (excess sweating), hypertension and chills. ([540])

POTS SYNDROME (Postural tachycardia syndrome)

Orthostatic intolerance is quite a common problem. This refers to changes in body position. Normally, the body responds to this by stabilising blood pressure etc. within 60 seconds. This is accomplished by changes in heart rate (increase of 10-15 beats/minute) and blood pressure.
However, in people with orthostatic intolerance, there is excessive heart rate increase on standing up. There will therefore be an impact on the cardiovascular system as a whole as well as in hormone levels involved with blood pressure regulation.
This may give rise to the following symptoms:

- Excessive fatigue
- Exercise intolerance
- Recurrent syncope (fainting) or near syncope
- Dizziness
- Nausea
- Tachycardia (rapid heartbeat)
- Palpitations
- Chest discomfort
- Shortness of breath
- Weakness - most noticeable in the legs
- Visual Disturbances: blurred vision/tunnel vision/'greying out'
- Gastrointestinal problems
- Migraines and other headaches
- Feeling tremulous
- Mood Swings

A recent study ([541]) of women with FMS has shown that they have an impaired ability to activate the hypothalamic-pituitary portion of the hypothalamic-pituitary-adrenal axis as well as the sympathoadrenal system, leading to reduced ACTH and epinephrine responses to hypoglycaemia. This may well also be the case in arachnoiditis patients.
Neurally mediated hypotension (NMH) is known to be associated with Chronic Fatigue Syndrome (CFS).
Very rarely, there may be autonomic dysreflexia as seen in spinal cord injuries, with paroxysmal hypertension due to excess sympathetic activity reflexly activated by bladder or bowel distension, as described by various authors. ([542])
Other cardiovascular symptoms include palpitations.

Bladder, bowel, and, sexual dysfunction: These are often very distressing to patients. 68% of survey respondents experienced this type of problem.

BLADDER DYSFUNCTION

The bladder has somatic, parasympathetic, and sympathetic innervation. In other words, it has input from higher centres (brain) provided that the pathways via the spinal cord are undamaged and also autonomic control.

The **pudendal nerve** is the somatic component of bladder innervation and innervates the external sphincter. When stimulated, it produces contraction of the external urethral sphincter, which is only able to remain tightly contracted for a short period of time. This sphincter normally contracts with transient increases in abdominal pressure such as when there is coughing sneezing, and laughing.

The parasympathetic nerve fibres arise from sacral segments S2-4, innervating the detrusor muscle. when the individual desires micturition. When stimulated by a need to empty the bladder (voluntary control), the detrusor contracts resulting in raised pressure within the bladder.

The internal urinary sphincter is innervated by the sympathetic nervous system, nerves originating from the thoracolumbar region. When stimulated, the internal sphincter relaxes.

As urine fills the bladder via the ureters (tubes which come down from the kidneys), the bladder wall muscle (detrusor) stretches allowing the bladder to expand; as the bladder fills, stretch receptors within the bladder wall are stimulated, sending the brain information as to the amount of urine in the bladder. Approximately 300 cc of urine within the bladder is necessary before the pressure within the bladder rises enough for the brain to recognize a sense of bladder fullness. With low bladder volumes, the sympathetic nervous system is stimulated and parasympathetic system is inhibited resulting in internal sphincter contraction and detrusor relaxation. When the bladder is full and micturition is desired, the inhibitory signals from the brain are replaced by impulses, which stimulate the parasympathetic system resulting in detrusor contraction, and inhibit the sympathetic system resulting in internal sphincter relaxation. The bladder pressure then rises to a point at which it exceeds the resistance within the urethra (the tube through which the urine leaves the bladder), and urine flows out.

Once the bladder has emptied, the brain again sends impulses restoring parasympathetic inhibition and sympathetic stimulation resulting in detrusor relaxation and internal sphincter contraction.

A severe lesion in the **cauda equina** (at the lower end of the spinal cord) affects bladder and bowel function as a result of damage to the **sacral parasympathetic outflow**. The detrusor muscle of the bladder is affected and reflex connection no longer occurs in response to distension. The bladder wall itself has a certain amount of elasticity, and with rising bladder pressure this forces some urine into the urethra.

However, the unopposed sympathetic supply to the sphincter muscle keeps it contracted and closed, and dribbling incontinence occurs. A similar situation arises with regard to the bowel and anal sphincter.

Damage further up the spinal cord, in which voluntary control of the bowel and bladder is affected, but which does not affect the parasympathetic outflow leads to an automatic bladder. Any voluntary aspect to the control of the bladder is lost, leading to "accidents".

Note that certain medications used in arachnoiditis patients may affect bladder function. For instance, antidepressants such as amitriptyline have anticholinergic effects, inhibiting detrusor muscle function. This may lead to some difficulty in initiating urination and possibly in emptying the bladder fully.

Aldrete looked at bladder dysfunction in arachnoiditis in detail:

	Females %	Males %
Dysuria	62	45
Hesitation	35	42
Incomplete bladder emptying	70	64
Frequency	78	46
Urgency	86	48
Incontinence	65	19
Self-catheterising	4.8%	0
Rectal incontinence	20	6

Types of bladder dysfunction:

1. Urgency: a sudden urge to empty the bladder; confusingly, this may arise when there is partially reduced sensation of bladder fullness, which is quite a common problem in arachnoiditis. This is because there is a delay in perception and an overblown response, which can make the urge quite painful.
2. Frequency: the need to pass water more often than usual (up to 8 times in 24 hours is about normal), often passing small volumes. This may be associated with an infection, especially if passing water is painful.
3. Hesitancy: inability to initiate a stream of urine; more usually in men, can be a sign of prostate enlargement. It can also be associated with spinal problems or a side effect of medication such as antidepressants (especially tricyclics like amitriptyline).
4. Retention: inability to empty the bladder; acute retention is obvious and very painful if untreated; chronically it may arise unnoticed (especially if there is loss of sensation), with a gradual build-up of retained urine. There is increased susceptibility to infection.

5. Dribbling: when the stream of urine does not cut off normally but continues to drip or dribble. There may also be constant incontinence if the bladder sphincter is damaged and unable to hold the urine in the bladder
6. Incontinence: (a) irritable/unstable bladder (detrusor instability): a feeling of urgency may be accompanied by wetting; this can also happen if the bowel is overfull; (b) reflex incontinence: loss of sensation of bladder fullness and interruption of the messages to the brain may cause it to empty by reflex activity (initiated at a spinal level) which is usually over-ruled by messages from the brain. (c) overflow: weak muscles due to disrupted nerve impulses fail to empty the bladder properly and it becomes large and floppy, able to hold large amounts of urine but leaking slightly (dribbling) (d) stress incontinence: weakened pelvic floor muscles mean that the sling which holds the bladder position is ineffective and when the bladder is full, a cough or a sneeze may allow urine to pass out.
7. Neurogenic bladder: (a) spastic: unstable bladder; (b) flaccid 'lazy' bladder fails to empty (c) dyssynergic: 'conflicting' bladder: muscles of the bladder wall and sphincter no longer co-ordinate; symptoms include urgency followed by hesitancy, dribbling or incontinence. If the bladder muscle contracts but the sphincter fails to open, there is a risk of urine reflux back up to the kidneys, which can eventually cause damage.

Urinary tract infection:

Loss of bladder function renders the individual more prone to urinary infection. This occurs particularly in those who have residual urine in the bladder after voiding. Careful attention to hygiene, especially if catheter use is necessary, is an essential preventive measure.

SEXUAL DYSFUNCTION: Sexual dysfunction in men included in Aldrete's survey: loss of libido (88%), partial impotence (63%), complete impotence (36%), 'difficulty arousing' (73%), penile pain during erection (38%).

Sexual function relies upon a delicate interplay between the sympathetic and parasympathetic nervous systems and also with some higher input (although the efficacy of the latter may diminish with age). Sexual dysfunction may affect potency and ejaculation in men, as well as causing problems with orgasm in both sexes.

This may happen as a direct result of arachnoiditis scarring in the lumbosacral region (particularly the cauda equina) or may be related to treatment, particularly with antidepressant drugs.

Drugs that cause sexual dysfunction:

Those commonly taken by patients with arachnoiditis include:

Alprazolam, amitriptyline, atenolol, baclofen, buspirone, carbamazepine, clonidine, diazepam, fluoxetine, gabapentin, indomethacin, methadone, mexiletine, naproxen, nefazodone, nortriptyline, oxybutynin, paroxetine, sertraline, trazodone, and venlafaxine.
Note that SSRI drugs are particularly known for this problem. (See below under Treatment.)

Loss of libido may also result from depression.

Neurogenic Bowel

Longstanding spinal conditions can cause neurogenic bowel problems, the type depending on the site of the damage. Arachnoiditis tends to affect the nerve roots primarily rather than the spinal cord, although that can be affected secondarily in some cases.
A complete injury at the cauda equina level (lower motor neurone) would cause areflexic bowel in which no reflex peristalsis (the propulsion of the contents of the gut) occurs. Nerves within the colon wall co-ordinate slow stool propulsion and the denervated anal sphincter has low tone. This results in a sluggish stool movement, a dryer, rounder stool, and a greater risk of faecal incontinence through the flaccid anal sphincter.
A reflexic bowel by contrast, resulting from an injury above the sacral spinal segments (Upper motor neurone) involves a sphincter that is spastic (increased tone). Defaecation cannot be initiated by voluntary relaxation of the sphincter. However, nerve connections between the spine and the gut are intact and there remains a reflexic co-ordination of stool propulsion.
Associated problems include:

- Haemorrhoids
- Abdominal distension
- Autonomic dysreflexia
- Difficulty with bowel evacuation
- Poorly localised abdominal pain
- Faecal impaction
- Rectal bleeding
- Constipation

Those with a lesser degree of damage may find they have some loss of rectal sensation, perhaps coupled with a visceral Hyperpathia (heightened pain, e.g. abdominal cramps with constipation). This means that there is a delayed perception of the full rectum and that once the threshold for perception of rectal distension is reached; there is sudden, painful (often burning) urge to defaecate, which may result in incontinence.
Faecal incontinence is highly distressing. It may involve loss of control of both flatus (gas) and faeces, and there may be leakage of either. Neuropathic incontinence can arise in arachnoiditis affecting the cauda

equina. Pelvic floor denervation secondary to childbirth or as a result of spinal cord or cauda equina damage will contribute to the problem.

Sudomotor effects of hyperhidrosis or anhydrosis (increased or absent sweating) may impact on temperature regulation, which is a common problem. Hyperhidrosis may be compensatory for loss of sweating in another area, or may be the initial phase before progression to anhydrosis.
Aldrete found an 80% incidence of 'profuse diaphoresis' and 42% nocturnal diaphoresis. The Global survey reported 63% of respondents with increased sweating.

Excessive sweating (hyperhidrosis or diaphoresis) occurs when the sympathetic nervous system is running on overdrive. This seems to be a common problem in arachnoiditis, and is probably in part due to direct effects on the sympathetic chain, which runs alongside the spine, and also partly due to the chronic stress of unremitting pain. A further reason might be that arachnoiditis patients can experience intermittent low-grade fevers and the sweating (especially at night) might be related to this. It should be noted that sweating could occur regardless of environmental temperature (even in the cold) or emotional state; *cold sweats* are often quite profuse.

Couto de Silva et al ([543]) described a case of arachnoiditis featuring body temperature disturbances and diaphoresis. The patient had "aberrant skin temperature and sweating" in different parts of the body.

Causes:
1. Primary = essential = idiopathic: cause unknown
2. Secondary: to conditions such as hyperthyroidism (overactive thyroid); menopausal

Primary hyperhidrosis is much more common in the general population than secondary: it usually starts in childhood or adolescence and persists throughout adult life. Locations include the face, armpits, palms and soles of the feet. It can be a highly distressing condition. Scalp/facial sweating may also be associated with blushing; axillary (armpit) sweating can lead to telltale staining on clothes and a rapidly developing strong body odour which can make socialising difficult. Primary hyperhidrosis occurs in up to 1% of the population.

Secondary hyperhidrosis in arachnoiditis: Heat intolerance seems to be a related problem: in Aldrete's survey, 91% of respondents experienced this (in the Global survey the figure was 58%). Low-grade fever occurred in 70% (28% in Global survey).
Clearly this is a common problem.

Spinal cord injury patients may suffer from **non-thermoregulatory reflex sweating**, which is due to unchecked spinal cord activity. Sweating is a function that allows body temperature to be maintained, but

in these patients, reflexive sweating occurs. It is often precipitated by stimuli such as emptying the bladder or bowel.

Compensatory sweating may occur if there is an area in which sweating is lost. Anhydrosis (absence of sweating) may occur in certain circumstances, including sympathectomy (see below).

Hyperhidrosis (excessive sweating) may also be a prelude to loss of sweating.

There is a peculiar condition called **gustatory sweating** (Frey's syndrome) which occurs in the face when salivary gland activity is stimulated by food.

An uncommon problem may be facial pain, loss of sweating on one side of the face and change in size of one pupil (Horner's syndrome). There are also isolated reports of Adie's tonic pupil.
Swelling (oedema) of the limbs (as in reflex sympathetic dystrophy RSD) is seen in some patients. However, it is difficult to assess whether this is a direct effect of arachnoiditis or a side effect of treatments such as intraspinal opiates (see below).

HYPERTHERMIA:
In Complex Regional Pain Syndrome, CRPS (see below*), damage to the sympathetic vasoconstrictive function which affects blood vessels, can lead to localised hyperthermia (raised temperature). This can lead on to hyperthermia in referred pain areas in other words, to more generalised raised temperature.
Note that opiate medication (morphine and related drugs) can cause facial flushing, as can antidepressants such as amitriptyline.
It is difficult to satisfactorily explain the highly common experience of wildly fluctuating body temperature that arachnoiditis sufferers undergo. Many people describe swinging from 'freezing' to 'boiling' within minutes and then back again. The likelihood is that this relates to abnormal autonomic function, and is similar to the fluctuations in blood pressure mentioned below.

*Arachnoiditis may be considered a type of CRPS (Type II). CRPS (Type I) is also known as Reflex Sympathetic Dystrophy and is a localised version usually affecting one limb extremity. Both types are characterised by: *severe burning pain* spontaneous and disproportionate to the trigger event; continuous and made worse by movement and touch, allodynia/*hyperaesthesia, localised swelling* which may cause nerve compression which is similar to and can be confused with carpal tunnel (at the wrist) or tarsal tunnel (foot) syndrome or indeed, thoracic outlet syndrome, which affects the whole arm and hand (pain, pins and needles, weakness, numbness); *sweating/absence of sweating*, c*hanges in skin colour/ temperature* (later

stages affect skin tone): initially warm, red and dry, later cyanotic (bluish), cold and sweaty, later still, in Stage III, it may be cool, glossy, pale or bluish. This is due to neurogenic inflammation. Then there may be: *hair growth* changes, *muscle spasms, dystonia* (abnormal muscle tone) and tremor. Later stages: *loss of bone density* may occur (Sudek's Atrophy), *joint tenderness and swelling*; causing reduced mobility; *Skin rashes* (including neurodermatitis) and nodules. The affected part may not feel 'part of the body any longer', leading to a *tendency to 'neglect'* (inattention to) this affected part therefore the patient may drop objects if hand affected or trip over if foot affected.

Type II CRPS also involves development of *secondary problems such as headaches* and later stages may involve *myoclonic jerks* as well as *atonic falling attacks; bouts of unexplained fever,* Interstitial cystitis.

RAYNAUD'S PHENOMENON

This is a condition in which the blood supply to the extremities, in particular the fingers and toes, but also the nose and ears, is interrupted by spasm in the blood vessels.

Episodes cause the affected part to turn first white, then blue and finally red.

Attacks are often triggered by touching something cold, or by exposure to cold conditions. Operators of vibratory tools may be affected and smoking is a factor.

Secondary Raynaud's is associated with conditions such as Sjogren's, Rheumatoid arthritis and Systemic Lupus, which are seen in a few people with arachnoiditis.

It may be that the attacks represent excessive sympathetic activity in the localised areas.

26 cases (out of 317) of Raynaud's were seen in the global survey.

PANIC ATTACKS

When we look at the effects of a sudden outpouring of adrenaline, we can see that they can include a highly unpleasant experience with some emotional component. This is not to suggest that the attacks are emotional in origin, rather the reverse, that the physical (physiological) disturbance has emotional effects. It is easy for this to be misconstrued by both the sufferer and their medical staff, especially in the context of a chronic, unremitting illness and sometimes an element of depression that is an entirely reasonable response to the situation.

Whether or not panic attacks are triggered by physical responses, it is vital to realise that they are, whilst frightening (adrenaline was designed to have that effect) they are not life threatening. However, if anyone is experiencing regular attacks, it may be worthwhile checking out current medication and also assessing any possible physiological causes, before assuming that these are an expected feature of the psychological effects of chronic illness.

GASTROPARESIS

This condition is seen in some diabetic patients, but I have also come across a few cases in arachnoiditis patients.

The principal features of this condition include:

- Nausea after meals
- Vomiting: especially undigested food in the middle of the night/ before breakfast; vomiting food eaten more than 4 hours previously
- Bloating
- Feeling full after only a few mouthfuls
- Loss of appetite

Autonomic dysreflexia (AD):

This is also known as hyperreflexia. It occurs in quadriplegic individuals (injury above T6). It indicates that the sympathetic nervous system is out of control. I have come across isolated cases of arachnoiditis in which AD has caused severe problems. These must have arisen due to damage to the connections between the sympathetic nervous system and the brain.

AD occurs when there is a source of irritation, pain or stimulus to the nervous system below the level of injury; the irritated area sends out a distress signal to the brain but it does not reach it; a reflex action occurs, contracting the blood vessels and causing a rise in blood pressure. Should this rise too high, there is a risk of seizure, stroke or even death.

AD attacks commonly arise due to one of the following causes:

1. Overdistended bladder: too much urine has accumulated and the bladder urgently needs draining
2. Retained stool in the lower bowel (constipation)
3. Pressure on the skin
4. Trauma
5. Infection
6. Temperature changes
7. Menstrual cramps
8. Pressure on genitals during sexual activity
9. Medical tests such as cystoscopy or gynaecological exam.

AD can be a medical emergency. Whilst it is rare in arachnoiditis patients, given the risk of stroke from an attack, I feel it warrants a mention in this article.

An attack of AD typically causes a sudden severe headache along with very high blood pressure.

<u>Symptoms:</u>

- Pounding headache

- See spots or blurred vision
- Nasal stuffiness
- Flushed face
- Red blotching on chest
- Sweating above the level of injury
- Goose bumps
- Clammy, cool skin
- Nausea
- Feeling anxious

A condition termed: **orthostatic hypotension-induced autonomic dysreflexia** is seen in chronic cervical myelopathy (damage to spinal nerve roots in the neck).
This occurs when blood pressure falls, perhaps when changing posture suddenly, or in hot surroundings. The symptoms mentioned above might all occur.

Exacerbating factors:

- Rapid positional change
- Morning (due to overnight recumbency)
- Large meals
- Warm environment
- Cough
- Emptying bladder
- Opening bowels
- Exertion
- Medication that causes blood vessel dilation

Swelling (oedema) of the limbs (c.f. reflex sympathetic dystrophy RSD) is seen in some patients. However, it is difficult to assess whether this is a direct effect of arachnoiditis or a side effect of treatments such as intraspinal opiates. (See below) It may be in part due to muscle weakness in the calves (due to nerve damage), which leads to inefficient venous return. It may be neurogenic oedema such as that seen in diabetic autonomic failure ([544]).
Some patients develop lymphoedema of the lower limbs and may suffer from recurrent cellulitis, or occasionally, venous ulcers as seen in diabetic peripheral neuropathy.

Symptoms reflecting inflammation

Aldrete has suggested that the prognosis "depends on the progression and extent of the irritative process on the arachnoid" and the resulting inflammation. He contends that "the majority of patients end up with a poor prognosis, due to the lack of an effective treatment to decrease the inflammatory lesions."([545])

He also describes varying presentations of the inflammatory aspect, gradual, intermittent or fulminant.

Most arachnoiditis sufferers experience a fluctuating course of symptoms, with intermittent "flare-ups" and periods of relative remission. These are suggestive of an inflammatory component to the condition.

Some sufferers have **intermittent low-grade fevers**, malaise and raised ESR (SED) and/or white cell count. These laboratory indices are both indicative of a non-specific inflammatory process. Auld ([546]) mentions fever and chills as part of the syndrome of chronic spinal arachnoiditis.

Aldrete found that 70% of his survey respondents had low-grade fever of unknown origin.

They may also have lymphadenopathy (enlarged lymph glands). Skin rashes of varying types are also quite common.

Such symptoms also occur in autoimmune conditions, and two possible links have been postulated:

1. Some sufferers from arachnoiditis may have a predisposition towards the development of autoimmune conditions.
2. The development of the arachnoiditis itself could in some sufferers also have an **autoimmune component**.

Other symptoms that may reflect an autoimmune aetiology are:

Skin rashes are a fairly common feature in arachnoiditis patients.

Skin rash may be urticarial (hives) or there may be angio-oedema, both suggestive of an allergic-type reaction. A few patients develop photosensitivity, but this may be related to medication (especially anticonvulsants). Aldrete found that 11.7% of his patients had skin rash, whereas in the global survey, 32% of respondents reported rash.

They can arise for a wide variety of reasons and in some cases; the rash may be unrelated to the arachnoiditis.

The main types of skin rash that one might expect in arachnoiditis are:

1. **Drug-related : see below**
2. **Allergic**
3. **Heat rash**
4. **Related to associated conditions such as lupus**
5. **Infective (lowered resistance to infection in chronic illness**
6. **Contact/irritant skin reaction (contact dermatitis)**

Drug related:

(i) Anticonvulsants: Skin reactions to anticonvulsants are relatively uncommon.

Morbilliform reactions are the most common. Most reactions, such as photosensitivity, are mild, but severe and life-threatening reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis and anticonvulsant hypersensitivity syndrome can also occur.
Gabapentin has not been reported as causing skin reactions as yet, whereas Carbamazepine is the commonest drug implicated in a variety of drug eruptions.
Lamotrigine can cause a rash if introduced at too high a dose.
(ii) Non-steroidal anti-inflammatory drugs can cause a variety of skin reactions:
Ibuprofen: vasculitis; Naprosyn: generalised blistering; Sulindac: blistering and other eruptions
Piroxicam: hand blisters
(iii) Psychotropic drugs: can cause various skin rashes:
Erythema multiforme - diazepam overdose, fluoxetine, sertraline, carbamazepine
Morbilliform - Carbamazepine, trazodone, desipramine, fluoxetine, alprazolam, bupropion, nefazodone, risperidone, chlorpromazine,
Photosensitivity - imipramine, doxepin, tricyclics, amitriptyline
Pigmentation - amitriptyline and diazepam following dermabrasion
Urticaria - trazodone, fluoxetine, imipramine, and chlordiazepoxide

Joint pains are also common, not just in weight bearing joints, but also small joints. 72% of the global survey respondents reported joint pains.
Rarely, there may be neurogenic arthropathy (Charcot joint), due to loss of sensation around the joint. This is also seen in peripheral neuropathies such as diabetic neuropathy.

A number of patients (58% in the global survey) complain of **dry eyes and mouth** (as in Sjogren's syndrome) but this is most likely to be due to side effects of medication. Other eye problems include iritis and uveitis, both inflammatory conditions seen also in association with autoimmune diseases.

Concomitant autoimmune conditions

A minority of patients also have an additional diagnosis of an autoimmune disease as well as their diagnosis of arachnoiditis. Autoimmune diseases seen in the Global survey included Systemic Lupus Erythematosus (5), Sjogren's syndrome (5), Type 1 Diabetes Mellitus (12); Thyroiditis / Hypothyroidism (20), Sweet's syndrome, Rheumatoid Arthritis (23), Polymyalgia Rheumatica (4); Primary Biliary Cirrhosis and Crohn's disease.

This is an area for further investigation. There seems to be a particular link between arachnoiditis secondary to myelogram dye and thyroid disorders. This is likely to be due to the high iodine contact in the dye. Symptoms of thyroid disorder are notoriously overlooked because they are insidious.
Hypothyroidism (low thyroid levels) presents with weight gain, feeling tired and lethargic, rough skin and hair, hoarse voice. Hyperthyroidism tends to cause weight loss, hyperactivity, anxiety and sometimes eye

problems (eyes look bulging). In any type of thyroid disorder there may be a goitre, which presents as a lump in the front of the neck that may cause problems swallowing.

Professor Duncan Topliss, Director of the Department of Endocrinology in Melbourne, Australia, wrote a short article for the Australian Thyroid Foundation ([547]), in which he remarked:
"Whereas the normal thyroid gland is tolerant of substantial excess iodine intake, the diseased thyroid is not. Either hyperthyroidism or hypothyroidism can occur depending upon the underlying thyroid problem."
He goes on to comment:
"Therefore it is recommended that if thyroid disease is present then iodine-containing medications be avoided if possible. *This includes x-ray contrast (dye) injections unless absolutely necessary*." (My emphasis)

He also states "Very high iodine intake can rarely provoke blood vessel inflammation (vasculitis), an effect independent of the thyroid." (I note that there are some individuals with arachnoiditis who either have diagnosed vasculitis or symptoms suggestive of this condition.)

Dr. Noel Rose ([548]) has written about iodine, linking it with autoimmune thyroiditis. Indeed, he cites contrast agents as one of the sources of iodine that may be linked to the increasing incidence this condition.
There are a number of papers in the medical literature that cite iodinated contrast agents as causative factors in thyroid disease. For instance, Meurisse et al, in Belgium, ([549]) include "radiologic contrast agents" as a cause of "iodine-induced hyperthyroidism".

Rose made a most pertinent remark:
"Because autoimmune disease can affect virtually any organ of the body, its manifestations are protean. Autoimmune diseases therefore tend to be treated by physicians from many different specialties."

I would add a rider:
The patient may well, on the other hand, 'fall between two stools', so to speak, and end up with poorly co-ordinated management of multiple problems and little continuity of care. This in turn can lead to misdiagnosis or missed diagnosis.

A small number of sufferers develop multiple drug **allergies**, a condition that is also seen in autoimmune conditions such as lupus. 25% of the global survey respondents reported this problem.

Note: a recent paper ([550]) on small fibre neuropathy noted that this common disorder is often "idiopathic" although autoimmune mechanisms are often suspected. Typically, it presents with painful feet in patients over the age of 60. Burning feet are common in arachnoiditis. Known causes of this condition include diabetes mellitus, amyloidosis, toxins, as well as inherited sensory and autonomic neuropathies. It is conceivable that there is a link between this condition and arachnoiditis.

General symptoms

Fatigue is a very common complaint, and can be due to a variety of factors. One of the commonest is insomnia, which is usually related to an increase of pain at night. Many arachnoiditis patients find sleep difficult and they may have some reversal of day-night pattern. Fatigue is also of course a feature of autoimmune conditions and in multiple sclerosis, which as we have seen, have similarities to arachnoiditis. Fatigue in arachnoiditis may be episodic or continual. It should be noted that depression is associated with a lack of energy and this may well be compounding the problem.

'Tiredness' was reported in 92% of respondents in the New Zealand survey, 76% in the global survey, and 56% in Aldrete's survey. In the New Zealand survey, 48% had moderate tiredness, 38% severe and 6% extreme.

Sleep disturbance is understandably common, and usually directly related to pain, which tends to be worse at night. It may contribute to depression, which is an understandable reaction to intractable pain, loss of function, loss of role and job, financial and relationship problems as seen in other chronic, debilitating conditions. Fear for the future (prognosis cannot be predicted) and uncertainty about the diagnosis substantially increase this problem. In the Global survey, 84% had disturbed sleep.

Heat intolerance: this common symptom is similar to the problems experienced by patients with Multiple Sclerosis. Hot conditions (e.g. a hot bath) exacerbate pain, weakness and other symptoms. 91% of Aldrete's survey and 58% of the Global survey respondents reported this symptom.

Weight gain occurs frequently (50% of the global survey respondents). This is largely to do with decreased mobility and may also be secondary to medication, particularly drugs such as: amitriptyline, gabapentin, ibuprofen, morphine and other opiates, prednisolone & methylprednisolone. Increased weight may of course result in further loss of mobility and puts undue stress on the joints of the lower body, exacerbating joint pain and if there is weakness, increasing the risk of falls.
Alternatively, some patients may suffer weight loss, due to general debility and often, poor appetite.

The **cognitive effects** of arachnoiditis are anxiety and reduced ability to think clearly, with some short-term memory impairment. These are usually in direct proportion to the pain level being experienced. ([551]) They may be compounded by the side effects from various types of medication, especially in combination.

In the Global survey, 63% of respondents reported this problem. 55% of the New Zealand survey respondents reported 'poor concentration'.

Depression and Anxiety: Many sufferers are reluctant to admit to depression, as they fear that doctors may more readily dismiss their more unusual symptoms as being a product of their mental state. However, it is an inevitable fact that a debilitating illness such as arachnoiditis has a substantial effect on psychological well being. Anxiety and depression are understandably common problems, but often help is not sought for this aspect of the illness. 62% of the Global survey respondents reported this problem.

Miscellaneous problems:

Osteoporosis:

Osteoporosis is a common condition that involves loss of mineralised bone mass in the skeleton, with resulting bone fragility and higher fracture risk. In the UK, osteoporosis affects 1 in 3 women and 1 in 12 men. Figures suggest that there is a fracture due to osteoporosis every 3 minutes, the hip being the commonest site.

Risk factors for osteoporosis include: post-menopause, low body weight to height, increased liability to falls, chronic disease affecting hormone levels, immobility, thyroid disease, suboptimal diet, cigarettes, caffeine and alcohol. Medication, especially steroids, is another important factor. Antacids, which may be taken by arachnoiditis patients on NSAID medication to alleviate side effects (heartburn etc.), are also implicated as they interfere with calcium metabolism.

Blood clots:

The deep veins in the lower leg are responsible for returning the blood to the heart; this function relies heavily upon the muscles in the calf to assist the movement against gravity. Obviously, when there is relative or complete immobility, this impairs the circulation considerably and allows pooling of the blood in the lower legs, thereby raising the risk of clotting.

Generally, this is not a serious problem unless a piece of a clot breaks off (becomes an embolism) and travels to the lungs, where it can be potentially fatal (pulmonary embolism).

In arachnoiditis, total paralysis is uncommon. It is therefore vital to maintain whatever mobility is possible in order to prevent thrombosis.

Low potassium:

There are a number of possible causes:

- Low potassium can occur for many reasons. Use of certain medication, diarrhoea and/or vomiting, and chronic laxative use (often as a result of constipation due to medication) are the most common. Decreased intake or malnutrition can also be a factor.

- Effect of medicines
    - Water pills (diuretics)
    - Medicines used for asthma or emphysema (beta-adrenergic agonist type of drugs such as bronchodilators, steroids, or theophylline)
    - Aminoglycosides (a type of antibiotic used for treating certain serious infections)
    - Insulin

Kidney losses can occur in conditions such as renal tubular acidosis, or in magnesium deficiency or leukaemia

Low levels of this electrolyte cause the following symptoms, which are often mild and non-specific, and may be multiple involving different parts of the body.

- Weakness, tiredness, or cramping in arm or leg muscles, sometimes severe enough to cause inability to move arms or legs due to weakness (like a paralysis)
- Tingling/ numbness
- Nausea/ vomiting
- Abdominal cramping, bloating
- Constipation
- Palpitations
- Passing large amounts of urine or feeling very thirsty most of the time
- Fainting due to low blood pressure
- Abnormal psychological behaviour (depression, psychosis, delirium), confusion or seeing or hearing things (hallucinations)

Chest pain mimicking angina

A number of arachnoiditis patients have experienced this symptom but investigation has excluded cardiac causes.

There are a number of possible reasons for this problem:

1. Referred pain from thoracic spine abnormality
2. Arachnoid cysts at the thoracic level have been noted to cause cardiac type symptoms (see above)
3. Musculoskeletal pain (e.g. intercostal muscle tenderness)
4. Upper gastrointestinal tract problems can cause non-cardiogenic chest pain that appears similar to angina (see below).

If in doubt, consult a doctor immediately. Serious causes such as myocardial infarction or pulmonary embolism may need to be excluded.

Dyspnoea (shortness of breath): may be associated with chest pain.

There may be a number of different reasons for this symptom, although arachnoiditis is only likely to be direct factor if it involves the thoracic region. Other causes include weight gain, loss of cardiopulmonary fitness due to immobility, incomplete ventilation (due to pain on breathing in, postural abnormalities, immobility etc.) and side effects of medication (respiratory depression from opiates, for example). Allergies associated with the condition may involve a respiratory reaction with bronchospasm, causing wheeze and shortness of breath (c.f. asthma).

Shortness of breath may also be associated with difficulty in swallowing and heartburn (see below).

A**cute onset of shortness of breath requires medical attention to exclude serious causes.**

Dysphagia:

Dysphagia (difficulty swallowing) may affect some patients (27% in the global survey), especially those who have cervical pathology. In particular, this may occur if there is arachnoiditis accompanied by degenerative changes such as anterior osteophytes (bony outgrowths). However, patients with only lumbar pathology may also experience it, though the reasons are unclear.

Pharyngeal symptoms may include feeling as if a lump is stuck in the throat, and this may be dismissed by some clinicians as “globus hystericus”, a psychosomatic complaint.

Difficulty swallowing causes a feeling that food or fluids ‘get stuck’ on the way down to the stomach. Swallowing is a precisely co-ordinated physiological process, which requires a series of sequential events to occur.

The commonest reason for dysphagia is ‘reflux oesophagitis’, in which the acidic contents of the stomach regurgitate back up into the gullet causing burning at the lower end (and sometimes ‘water brash’, a bitter taste in the mouth on bending over). Heartburn, as most people know it, is of course a well-known symptom. However, there may also be angina-type chest pain and shortness of breath (similar to asthma). Indeed, any adult who suddenly develops asthma-type symptoms should be investigated for reflux.

Reflux may be associated with a ‘hiatus hernia’, a defect in the diaphragm muscle, which leads to reflux on bending over or lying down flat (often in bed at night).

Left untreated, the acid reflux causes inflammation of the oesophagus which can lead to scarring and narrowing and hence, difficulty in swallowing. Note that NSAID (anti-inflammatory medication) use can exacerbate this type of problem.

Other similar causes include a pouch (diverticulum) in the oesophagus, in which food can become trapped.

In neurological conditions such as MS, there may be a neurological cause for dysphagia. There are 3 basic problems which can cause trouble in swallowing in the upper region:

1. Inco-ordination of the muscles of the mouth and throat, so passage of food backwards to the throat is inefficient.
2. Weakness of these muscles, making passage of food slow and difficult.

3. Loss of sensation

These may lead to choking or coughing when swallowing is attempted, or food may feel as if it is going down the windpipe.
Dry mouth secondary to medication may compound the problem.

Difficulty in swallowing liquids is usually due to poor muscle control before the swallow and may be associated with neurological conditions.
Difficulty swallowing solid food is usually due to abnormality in the structure or function of the muscles of the mouth or throat or damage to the lining of the gullet (as above).
Common symptoms include:

- Difficulty chewing and/or moving food to the back of the mouth
- Needing to spit out lumps of food
- Reluctance to eat/drink
- If talking with food in the mouth, forgetting to swallow causing spluttering
- Coughing/choking on food/drink
- Dribbling
- Feeling as is food/tablets are not going down or getting stuck in the throat
- Pain or pressure in the chest

Vocal changes may also occur: with a hoarse, 'wet' or 'gurgly' voice after swallowing, which may be due to vocal cord paralysis or to acid reflux.
Additional symptoms include weight loss, chronic chestiness or repeated chest infections.
NOTE: vomiting or regurgitation of blood or 'coffee grounds' requires urgent medical attention.

Recurrent sinusitis:
Again, this seems to be quite a common problem in arachnoiditis patients. One of the possible explanations is that the chronic stress of the illness leads to immune suppression and therefore susceptibility to infections. Airborne infections are the most widespread and thus the most likely.

Sleep apnoea: the prevalence of this has yet to be established. It should, however, be noted that this is one of the symptoms of Chiari malformation or cervical cord compression, which does not explain why it is seen in patients with only lumbar arachnoiditis. It may well be the result of abnormal nerve supply to the muscles of the larynx or pharynx.

Recurrent dental problems:
Dental problems are a common problem in arachnoiditis sufferers.

Mostly, people report dry mouth, soreness in the mouth, rapid dental decay and problems with dental local anaesthetics.

Many patients undergo repeated root canal procedures but continue to suffer from facial pain and odontalgia (tooth pain) without attributable dental pathology. There is an increase in tooth decay which may be linked with medication that causes dry mouth that in turn reduces the protective power of saliva. Pain also causes some people to grind their teeth (bruxism).

Many medications used to combat chronic pain cause dry mouth as a side effect. A dry mouth (xerostomia) is a common side effect with drugs such as antidepressants (e.g. amitriptyline), clonidine, propanolol, antihistamine, and drugs to treat bladder incontinence.

Rather than being considered a mild nuisance, this common occurrence should be recognised as a significant factor in inducing dental problems.

It is important to realise that saliva is an essential fluid in maintaining dental health. It acts as a protective agent against decay: it washes away sugars and it neutralises acid (which demineralises teeth). It also contains the minerals calcium and phosphate.

Other conditions that are associated with dry mouth include: Sjogren's syndrome, an autoimmune condition (note that there may well be an autoimmune component to arachnoiditis and there are a number of people with both conditions diagnosed). Generally, in Sjogren's there will also be dry eyes (the test for this condition is the Schirmer's test).

Other circumstances in which dry mouth can occur include chronic sinus problems (not uncommon in arachnoiditis: the reason being as yet unclear) because sufferers tend to breather through their mouths instead of their nose. Other condition affecting the patency of the nasal passages (e.g. deviated septum, adenoids) can lead to mouth breathing, especially at night. Radiotherapy in the neck region may destroy salivary glands.

Once someone experiences a dry mouth, they may fall into a cycle of actions that precipitates tooth decay. Often they will increase their fluid intake, perhaps using thirst quenching cool drinks, which are often full of sugar. Carbonated (fizzy) drinks not only contain sugar, even the sugar-free ones may have a damaging effect. Fruit juices (even pure) are doubly bad as they have sugar and acid. Taking frequent sips of these drinks compounds the problem.

Of course, it is also tempting to suck sweets to wet the mouth.

Note that opiate medication (morphine and related drugs) may cause cravings for sweets.

Dry mouth may also lead on to burning sensation. A burning tongue may be associated with smoking, menopause, candidal infection etc. Glossitis (pain and redness in the tongue) if acute may be associated with gingivitis (gum swelling) or a generalised stomatitis (inflamed mouth). Chronic glossitis may occur in chronic ill health (non-specific) anaemia and tooth infections, as well as conditions such as gastritis and during the use of some antibiotic drugs. The autoimmune condition pernicious anaemia is another cause arising due to vitamin B12 deficiency.

Burning Mouth Syndrome:

This uncommon condition (BMS) affects mostly postmenopausal women aged 50 or over.

The mechanism by which BMS occurs is yet to be understood.

However, there have been links noted between BMS and hormonal disturbances, salivary flow rates, medication side effects, immunological disorders, vascular and neurological disorders. Neuralgia and sensory disturbances may be involved. In a few cases, deficiency of vitamin B12 or folate may be found. Food allergy may be a precipitating factor. Smoking habits and alcohol consumption, though potentially factors, are rarely acknowledged as such.

However, for idiopathic BMS, no causative factor can be identified.

Triggers for arachnoiditis symptoms

The New Zealand survey looked at trigger events for symptoms:

Activity: 90% were aggravated (cf. Long 94% had back pain exacerbated by activity)

Position: prolonged sitting/standing etc.; crouching/bending. (~40% for each)

Therapies: physiotherapy, osteopathy, chiropractic, hydrotherapy, TENS were listed by 2 subjects only.

Weather and ambient temperature: 23% were affected.

Specific factors: including stress, intercurrent illness etc.

Unknown: 6 subjects were unable to identify trigger events.

Side effects of medication (see in detail below)

These occur to some extent in most arachnoiditis patients, largely because of the potent drugs involved, often used in combination. Opiates alone can cause a wide variety of side effects, but when taken in combination with adjuncts such as antidepressants; anticonvulsants or muscle relaxants; there may be a cumulative effect.

The most common side effects are dry mouth, constipation, drowsiness, nausea, dizziness, urinary retention and blurred vision. Some drugs, such as opiates, NSAIDS and certain antidepressants may cause fluid retention, and thus weight gain.

LIVING WITH ARACHNOIDITIS

Christine Hopkins, a New Zealand nurse, wrote a thesis in 1998 on "The Presenting symptoms associated with arachnoiditis and the experience of living with them in everyday life".

In this study, she interviewed in considerable depth, 11 participants, 1 of whom had no pain. The others experienced pain in various sites, burning, numb and cold areas, stabbing; flares of pain; constant; sore bones; 'ice burn', deep; cramping; intensifies with activity; 'not like any other sort of pain'; 'a freezing cold burn'. They also had headaches: linked to myelograms and epidural steroid injections.

In addition to their severe physical pain and impairment, the interviewees described the emotional aspects of living with this incurable illness.

"The study findings also indicate the complexity of the situations in which those with arachnoiditis find themselves." The participants' perceptions of their level of function reflected "a high level of disability linked largely to pain, as an immobilising factor in their lives." Hopkins also remarked on social isolation as a "marked feature of participants' lives".

Sufferer Janet Kraal wrote her story, which was published in the book "Released From the Web" in 1997. (Minerva Press).

Janet described the pain of arachnoiditis thus:
"It saps the strength and crowds the consciousness, until the person is overwhelmed and wishes quite simply for the release of death."

She wrote of living with arachnoiditis:
"It's hard to accept a condition which gives pain twenty-four hours a day. It's taxing on you mentally and one becomes exhausted with the pain, trying to do what may be the simplest of tasks. We are advised to try not to dwell on the pain, not to brood, to concentrate on other things, but when the pain is overwhelming one simply cannot be distracted or think of anything else... We feel trapped and helpless, we feel miserable, tense, angry and irritable."

Dr. Antonio Aldrete noted in his book, "Arachnoiditis, The Silent Epidemic": "Although symptoms of ARC are not specific, they are very real, and suffering patients bear these every day."

PROGNOSIS

Arachnoiditis has been described as an insidious disease that is incurable. Guyer's paper on the prognosis of arachnoiditis ([552]) suggests that there tends to be a spectrum of the course of the disease, which varies from mild and non-progressive, to a fulminating progression that may cause paralysis and even death. Wilkinson ([553]) believes that progression after the first 24 months is unlikely to be due to the disease process alone. Most authors state that its onset may be years after the precipitating cause.

The NZHTA Report noted: "There is a scarcity of literature dealing with the prognosis of arachnoiditis." The author also remarked that the prognosis was complicated by a variety of factors such as variable onset and spectrum of symptoms and difficulties in diagnosis and management as well as the original underlying spinal pathology.

In general, arachnoiditis presents a highly variable clinical picture, with a fluctuating course of remission and intermittent 'flare-ups'. Some patients seem to reach a "plateau" and stabilise without further deterioration, whereas there is a group of patients who develop a relatively rapid deterioration (within a matter of months) during which they tend to lose function in the affected limb(s). This tends to happen after a seemingly trivial event such as a minor fall or car accident.

Patients with retained oil-based myelogram dye may have either a thin diffuse film or localised encapsulated deposits. The latter may be disrupted by an event such as a minor car accident or a fall. Hence there may be sudden, seemingly inexplicable onset of symptoms even if there has been substantial interim period since the myelogram procedure (several years). An alternative explanation might be that trauma (or further surgery) involves blood within the epidural or subarachnoid space and as we have seen, this can act synergistically with a chemical agent present, or can, by itself, be irritant enough to precipitate clinically significant adhesive arachnoiditis.

Whilst Guyer suggests that life span is on average shortened by some 12 years, there is no literature covering a mortality rate from the condition. Of itself, the disease does not seem to be life-threatening, but a combination of high doses of analgesia and other drugs, prolonged immobility etc. have an undoubtedly deleterious effect on the body as a whole and may thus precipitate further morbidity and possibly mortality. Furthermore, the ongoing daily onslaught of pain and debility can lead to a severe depression and suicidal actions. A number of sufferers have taken their own lives, unable to live with the extent of the suffering involved.

IS ARACHNOIDITIS PROGRESSIVE?

This is a question that sufferers raise on a regular basis, and is an issue of major concern to them.

One must first bear in mind that occult or 'silent' arachnoiditis (without symptoms) may be present quite commonly in anyone who has experienced an event that can precipitate the pathological disease process, whether mechanical (surgery, trauma), chemical (injection) or infective (meningitis). There is, however, no actual data for the incidence of this silent type, and we are as yet unsure of the number of people walking around unaware of the hidden "Sword of Damocles" hanging over them.

One of the important questions is what turns the silent type of arachnoiditis into symptomatic adhesive arachnoiditis. Is it simply the degree of severity of the disease itself? As we have seen, this is not an easy question to answer. The syndrome of adhesive arachnoiditis may arise after a trigger event, often invasive, such as spinal surgery. This then would constitute a progression from silent arachnoiditis to symptomatic adhesive arachnoiditis. The exact level at which symptoms 'kick in' is unclear.

Having examined the wide variety of problems involved in the adhesive arachnoiditis **syndrome**, it is clear that there is more involved than simply arachnoiditis, the pathological disease process: we are dealing with a complex set of interacting problems.
It may be helpful to consider the syndrome as an arrangement of dominoes on their edges side by side. The disease process is the end domino and once that is given an impetus to topple, by a precipitating event, there will be an ongoing wave of dominoes falling, the number and speed depending on the strength of the

original impetus, and by how closely aligned the dominoes were. The individual dominoes represent different aspects of the syndrome, such as musculoskeletal problems, autonomic effects etc., which arise secondary to the arachnoiditis disease process.

In the absence of further exacerbating events, which, as we have seen, may provoke a more marked progression of symptoms due directly to the disease process, there are a number of ways in which the syndrome appears to progress:

1. The underlying spinal condition may progress (e.g. degenerative disc disease)
2. Musculoskeletal symptoms may increase over time, particularly if there is disuse atrophy and loss of mobility
3. Chronic pain affects the levels of stress hormones and the autonomic nervous system
4. Centralisation of pain.

These aspects of the condition are explained in further detail below in the Symptoms section.

The individuals who seem to far worst are those who:

- Mobilise in a limited way
- Require high levels of analgesic medication

This may of course reflect either (a) an initial severe level of the disease or (b) misguided attempts to reduce the risk of further damage. In the latter case, patients make the apparently rational assumption that pain=damage and that if exercise causes pain, that must mean more damage is being done. This is not in fact the case. Potentially, lack of exercise is far more likely to cause increasing problems such as disuse atrophy (muscle wasting) etc. than a sensible low-key exercise regime. Immobility carries a number of health risks of itself, including reduced cardiac fitness, weight gain, osteoporosis etc.
In addition, many people end up in the overactivity/under activity cycle: overdoing things then suffering from increased pain and being unable to do any exercise for a while. The importance of recognising this cycle and its impact upon quality of life is substantial if the disability cycle is to be broken. However, as central pain is often a feature of the adhesive arachnoiditis syndrome, a careful and balanced approach based upon good pain control must be adopted.

In summary, in the majority of cases of arachnoiditis the disease process remains a hidden entity.
In a minority, symptomatic adhesive arachnoiditis develops. Within that population, a further small number may develop progressive arachnoiditis (and even complications such as syringomyelia) usually as a result of a precipitating event.
The syndrome, however, arising mostly due to secondary effects, may tend to be progressive over time, but this does NOT necessarily reflect a progression of the arachnoiditis disease process itself.

Patients may well need reassurance of this, especially when there are new symptoms such as in the upper body.

However, sustained exacerbation or spread of symptoms should be investigated to exclude the possibility of complications or a treatable spinal problem, such as a disc fragment.

UNCOMMON COMPLICATIONS OF ADHESIVE ARACHNOIDITIS

1. Subarachnoid cysts
2. Syringomyelia
3. Communicating hydrocephalus

1. Subarachnoid (arachnoid) cysts: These are a recognised complication of arachnoiditis, in particular that caused by myelographic dyes or epidural anaesthesia. ([554];[555]) They tend to be more common in the thoracic region than cervical or lumbar. Kendall et al ([556]) stated that the incidence of cysts at myelography, as incidental findings, is relatively common, but rarely of clinical significance. In symptomatic cases, clinical presentation is generally non-specific, although there may be a sensory level, which is not a finding in uncomplicated arachnoiditis. Symptoms tend to be intermittent and may occur with postural changes or Valsalva manoeuvres (e.g. straining to empty the bowel). 30% of patients may have intermittent periods of remission but the majority of episodes tend to progressively worsen over time.

Surgical excision or drainage is often successful, provided that there is early intervention.

2. **Syringomyelia:** Whilst an uncommon sequela to arachnoiditis, syringomyelia should nevertheless be considered as a possible complication. Indeed, Kamada et al ([557]) recommend follow-up serial MRI imaging for patients with adhesive arachnoiditis in order to detect syringomyelia as early as possible.

Syrinx formation tends to occur in the segment of spinal cord adjacent to the area affected by arachnoiditis. It then starts to expand, due to pressure differences along the spine causing the fluid to move within the cavity. This is sometimes referred to as non-communicating syringomyelia.

The primary symptom of syringomyelia is pain, which may spread upward from the site of original pathology (the arachnoiditis lesion). Neurological deficit tends to be in a “cape-like” distribution in the upper part of the body. Increased levels of pain, increased spasticity and decreased physical function are often early indicators of syrinx development.

The principle features of syringomyelia are:

- Headache- worsens with cough, sneeze, and strain.
- Neckache
- Pain in upper limbs, often exacerbated by valsalva manoeuvres, exertion or coughing.

- Areas of dissociated sensory loss, which may be in a bizarre distribution over the trunk and upper limbs.
- Loss of temperature sensation in upper limbs may lead to painless burns.
- Loss of upper limb reflexes; positive Babinski reflex
- Atrophy (wasting) of small muscles in the hands
- Spastic paresis (increased muscle tone and weakness) gradually progressive, leading to difficulty in walking
- Uncoordinated movements
- Muscle spasms and fasciculations
- Skin rashes
- Alteration in sweating
- Raynaud's phenomenon (cold, painful hands due to poor circulation)
- Horner's syndrome (see above), nystagmus.
- Dysphagia (difficulty swallowing)
- Dysphonia (abnormal voice)
- Abnormal salivation.

(NB. These symptoms are sometimes seen in uncomplicated arachnoiditis. Jenik et al. stated that spinal cord syndromes due to non-traumatic adhesive arachnoiditis cause "predominantly syringomyelic sensory deficits.")

Later stages may affect bladder, bowel and sexual function.
Joint pains worse with straining.
Charcot Joints (neurogenic arthropathy= joint damage due to lack of protective sensation)
Symptoms may be unilateral or bilateral.
An uncommon finding is onset of electric shock sensation running up and down the spine when the head is flexed or extended, occasionally followed by syncope (passing out). This is known as Lhermitte's phenomenon.
Some patients may show an increasing scoliosis (lateral curvature of the spine) that is thought to be due to unequal nerve supply to the paraspinal muscles.

Misdiagnoses have included:

- Carpal tunnel syndrome (neurological symptoms resulting from compression of the median nerve at the wrist)
- Ulnar nerve compression (ulnar nerve in the arm)
- Cervical spondylosis (degenerative disease of the cervical spine).

3. Hydrocephalus: This is a rare complication, details of which are beyond the scope of this article. It tends to be of the communicating type.

Normal pressure hydrocephalus (NPH) is an accumulation of cerebrospinal fluid (CSF), which causes the ventricles of the brain to enlarge. This may not cause the increased intracranial pressure, seen with most types of hydrocephalus, but the abnormal accumulation of CSF is thought to stretch the nerve tissue of the brain causing a triad of symptoms. Normal pressure hydrocephalus is a misleading term because CSF pressure may fluctuate from high to normal to low.

Medical literature on hydrocephalus secondary to arachnoiditis is scant, but there are isolated reports. One of these ([558]) describes a case in which a combination of aseptic meningitis, arachnoiditis, communicating hydrocephalus and Guillain-Barre syndrome followed metrizamide myelography. Other causes include cranial surgery, subarachnoid haemorrhage, meningitis, tumour or cysts, subdural haematoma, bleeding during surgery and infections.

Poon et al. ([559]) recently reported on a case of spinal tuberculous arachnoiditis (thoracic) presenting with acute hydrocephalus presenting with confusion and fever, who needed treatment by shunting. Moling et al. ([560]) reported on a case of 14 months of chronic meningitis, ventriculitis, choroid plexitis, and lumbar arachnoiditis, complicated by acute hydrocephalus. Aspergillus organism was isolated from the cerebrospinal fluid of the patient, who had been a previously healthy man.

Uefuji ([561]) has described the case of a woman who had spinal anaesthesia for knee surgery and subsequently developed cauda equina inflammation and after 2 months, hydrocephalus and thoracolumbar arachnoiditis.

Sotelo et al., ([562]) from the National Institute of Neurology and Neurosurgery in Mexico City, have classified various forms of cystercicosis involving the brain, including active forms (ongoing infections) with meningeal irritation. In these cases there are increased mononuclear cells, protein in the CSF and positive CSF serology tests against cysticerci. Arachnoiditis is listed as one form and “meningeal irritation with hydrocephalus” as the second. (There are also various cystic forms). The authors cited a 3.8% incidence of hydrocephalus in their series of 753 cases of neurocystercicosis, and 48.2% incidence of arachnoiditis.

Symptoms of NPH

Normal pressure hydrocephalus has a presentation similar to that of dementia, Alzheimer’s disease, or other neurological disorders such as Parkinson’s syndrome. NPH normally occurs in adults 60-years and older, and in as many as 10% of all patients with symptoms of dementia.

Characteristic symptoms of normal pressure hydrocephalus are stuttering walk, urinary incontinence, ataxia and first traces of dementia and memory loss.

Gait: mild imbalance can result in an inability to stand or walk; there may be wide-based gaits, with shuffling, short, slow steps. There is often trouble picking up the feet that can lead to tripping. This tends to be the most pronounced and first apparent symptom.

Mild dementia: may manifest as a loss of interest in daily activities, forgetfulness, difficulty with routine tasks, short-term memory loss.

Impaired bladder control: urinary frequency and urgency may result in complete loss of control; there is a strong immediate urge to void; faecal incontinence may rarely occur.

DIFFERENTIAL DIAGNOSIS OF ADHESIVE ARACHNOIDITIS

The diagnosis of adhesive arachnoiditis requires the exclusion of other causes of Failed Back Surgery Syndrome, such as recurrent disc herniation, residual disc fragments, spinal stenosis, spondylosis of the spine, and epidural fibrosis. In particular, it is vital to identify treatable causes for pain and loss of function.

The most common spinal lesions associated with FBSS are:

- Instability
- Stenosis
- Recurrent disc herniation
- Missed lesions
- Intraneural fibrosis -- epidural fibrosis
- Arachnoiditis
- Soft tissue dysfunction
- Facet syndrome
- Internal disc disruption
- Pseudoarthrosis
- Adult tethered cord syndrome

Note that tethered cord syndrome is a treatable cause of FBSS. Yamada and Lonser ([563]) noted, "Too often, adult patients with TCS are misdiagnosed as having "failed back syndrome."" TCS manifests as severe back and leg pain, a subtle onset of motor/sensory changes and musculoskeletal deformities.

Other causes of polyneuropathy should also be considered, especially those of autoimmune origin (see above).

It is interesting to note that a number of patients have a dual diagnosis of arachnoiditis and multiple sclerosis (MS). This is presumably due to similarities between the two conditions.

Fibromyalgic symptoms are likely to be part of the arachnoiditis syndrome, as opposed to being due to a separate disease entity. Patients may have a dual diagnosis of arachnoiditis and fibromyalgia (or chronic fatigue). Features of myofascial pain and malaise are a common occurrence as part of the arachnoiditis syndrome.

Note that 70% of patients with FMS meet the CDC criteria for CFS *(Buchwald 1987)* and two thirds of patients with CFS meet the ACR criteria for FMS (*Goldenberg 1990b).* FMS and myofascial pain syndrome (MPS), while probably separate entities, often coexist *(Granges 1993).* It seems unlikely that these patients have three separate disease processes. There is obviously a considerable degree of overlap between these conditions.

Limb symptoms may have been previously diagnosed as Reflex Sympathetic Dystrophy (RSD).

The possibility of thyroid disorder should be especially borne in mind in patients who have a history of myelogram, whether oil-based or water-based, due to the high iodine content of the dyes involved.

Below is a brief list of some possible diagnoses that might be used instead of arachnoiditis:

Musculoskeletal

Facet joint

Degenerative disc disease, etc.

Fibromyalgia

Failed Back Surgery Syndrome

Disuse syndrome

Spinal stenosis

Epidural fibrosis

Neurologic

Post stroke pain syndrome

Peripheral neuropathy

Postherpetic neuralgia

Radiculopathy

Complex Regional Pain Syndrome

Multiple Sclerosis

Infectious

Cellulitis

Infectious arthritis

Vascular

Raynaud's disease

Rheumatic

Rheumatoid arthritis

Systemic lupus erythematosus

Psychiatric

Depression

Malingering

The similarity of arachnoiditis and CRPS

In broad outline, adhesive arachnoiditis, in particular the chemically-induced type could be categorised as Complex Regional Pain Syndrome Type II. (CRPSII), also known as causalgia.

Complex regional pain syndrome may be initiated by trauma or as an iatrogenic complication after surgical procedures such as arthroscopy and carpal tunnel release. Complex regional pain syndrome has also been reported following nerve injury caused by intramuscular injection or routine venepuncture and as an adverse reaction to subcutaneous allergy injections. In addition, the syndrome has been associated with medical conditions such as diabetic neuropathy and multiple sclerosis. The syndrome is estimated to occur in 1 to 5 percent of patients who have sustained peripheral nerve injury (type II).

The actual incidence of complex regional pain syndrome is unknown.

Reflex Sympathetic Dystrophy: (Complex Regional Pain Syndrome Type I): Causalgia

"If Hell were a clinical medical condition, it might look something like reflex sympathetic dystrophy or RSD."

Tom Haederle, Johns Hopkins University.

A number of patients who have a history of risk factors for arachnoiditis are diagnosed with **Reflex Sympathetic Dystrophy (RSD)**, which is also known as Complex Regional Pain Syndrome Type I. This is characterised by severe burning pain in a limb, occurring usually after trauma or surgery. There is often an element of allodynia and hyperpathia. Autonomic effects include sudomotor (sweating) and vasomotor (vascular) abnormalities. There are changes in limb temperature, discolouration and oedema. Later stages may involve joint stiffness, loss of mobility and osteopaenia or osteoporosis (loss of bone density), as well as skin texture and hair growth changes. The frequent occurrence of this condition in arachnoiditis suggests that the RSD type symptoms are in fact a part of the arachnoiditis syndrome, rather than a separate disease entity.

There are several cases in which arachnoiditis and RSD have both been diagnosed.

RSD is a disease of the nervous system that begins with involvement of the sympathetic nervous system in a limb, generally after relatively minor trauma, including surgery. Onset is typically within days or weeks of the event.

CRPS Type II (causalgia) is a more widespread phenomenon.

Arachnoiditis and Multiple Sclerosis

As we have seen, these two conditions share a number of features, notably nerve pain (often trigeminal neuralgia in MS), painful muscle spasms, spasticity and loss of function. These symptoms are often exacerbated by heat in both conditions.

A number of patients with arachnoiditis also have either an established or suspected diagnosis of MS. Unfortunately, one of the diagnostic tests for MS is a lumbar puncture, which is contraindicated in cases of arachnoiditis.

THE CLINICAL ASSESSMENT

In 1997, Congressman James Traficant submitted a Bill to the U. S. Congress ([564]) calling for a ban on myelogram dyes, and research into myelogram-related arachnoiditis and potential treatments. Traficant pointed out: "A large number of medical professionals do not know how to diagnose myelogram-related Arachnoiditis...lack of information prevents the physician from recognizing the disease."

It is vital for the assessing physician to take into account that adhesive arachnoiditis does not present with a discrete clinical picture and that there may be symptoms that at first glance appear unrelated to any proven pathology. In addition, the few tests available to assess the level of pathology are ineffective at representing the true impact of the condition upon a patient's life.

Sadly, a significant proportion of patients have had difficult previous experiences with the medical profession. Many have been labelled as having psychosomatic problems, although the Mensana study in 1993([565]) found that most chronic pain patients do have underlying organic pathology.

The Mensana authors stated: "Unfortunately, the psychiatric abnormalities that are the normal response to chronic pains tend to bias many physicians, resulting in less than extensive evaluations".
They go on to recommend a multidisciplinary approach, which they believe leads to improved diagnostic accuracy. Although the study does not refer specifically to arachnoiditis, this is a neurogenic pain syndrome that causes chronic pain, as do those conditions studied by Mensana.

Physician bias against patients involved in litigation, as well as female patients with chronic pain conditions ([566]) may still be encountered.

Previous consultations with overtly sceptical healthcare professionals may lead patients to be highly sensitive to the presence of such a bias. The iatrogenic nature of the condition is likely to occasion feelings of anger and resentment that can interfere with the therapeutic relationship. Over-assertive or highly anxious patients may need some reassurance that they are (finally) being taken seriously. It may therefore be unproductive for the doctor to assess the patient's personality and coping abilities within the first interview: this can be postponed until a good rapport has been established.
Historical information may be convoluted and patients are often poorly able to communicate the sequence of events and the current, usually diverse symptoms.
Examination may or may not reveal significant neurological deficit. However, the possibility of pain of central origin should be borne in mind even if there is no obvious clinically observable abnormality.

The presence of central sensitisation will confer poorly localised pain that does not conform to dermatomal distribution. It is likely to be dysaesthetic pain that is difficult for the patient to describe.

If the patient complains that it feels as if their legs are going to collapse, this may suggest an element of Central Pain with muscle spindle pain; this may be demonstrable by prolonged latency on somatosensory evoked potentials (SSEP), signifying posterior column damage. If SSEP is unavailable, examination can often detect subtle losses in vibratory sense with very exacting comparisons of tuning fork response, applying the tuning fork to a bone located under the area of greatest skin dysaesthesia. The examiner should allow the patient to indicate when vibration disappears, and then move the fork to a less dysaesthetic area for comparison.

Pathognomonic features of neuropathic pain are:

- Pain poorly localised
- Burning in nature
- May be felt in numb areas
- Worse at night
- May include allodynia

Signs may include areas of vasoconstriction (perceptibly colder skin) which represent vasomotor manifestations of neuropathic pain, myofascial trigger points may also be identified, particularly in the paravertebral region; the pilomotor reflex may well be hyperactive in affected areas causing 'goosebumps', particularly if a tender motor point is stimulated, and there may also be trophoedema (cellulite type or 'orange peel' appearance) or dermatomal hair loss may be apparent. The extent of nerve root involvement may be determined by use of the 'matchstick' test, in which the blank end of a matchstick is used to make firm indentations in the skin of the affected area which persist longer than those made in healthy, unaffected areas. ([567])

The conventional measurement of muscle strength can be insufficiently sensitive to detect significant weakness and fatigability. Perry has published two papers ([568]; [569]) about the limitations of manual testing for weakness and also discussing compensatory overuse of muscle groups in post polio syndrome, which shares some of the features of arachnoiditis. Perry states that "muscles with grade 5, 4 or even 3+ strength allow a person to move normally; the greater intensity of effort is unrecognised," and those studies show that "the mean strength of grade 4 muscles was approximately 40% of normal." This is also the case for arachnoiditis patients. There may occasionally be denervation hypertrophy of muscles instead of atrophy.

Now that agencies in the United States have urged doctors to consider pain as the 'Fifth Vital Sign' (alongside pulse, blood pressure, temperature etc.) the clinician clearly has a duty to fully assess a patient's pain level. Simply using pain scales, or using the more complex pain assessment questionnaires

may accomplish this objective. The NEUROPATHIC PAIN QUESTIONNAIRE from Krause and Backonja at the University of Wisconsin may be a helpful tool. This has discriminant function scores that predict neuropathic and non-neuropathic pain. ([570])

Clearly, it is vital to exclude treatable causes of the presenting symptoms. Having done this, the onus is on the clinician to maintain an active programme of medical care and a supportive doctor-patient relationship, to ensure that the unfortunate sufferers of arachnoiditis do not feel they have "just been left to get on with it."

DIAGNOSTIC TESTS

Who is the most appropriate specialist to assess and treat arachnoiditis? The short answer is, someone who has some experience of the condition. Practically speaking, this may mean that a local specialist who is familiar with arachnoiditis is hard to find. However, neurologists or rheumatologists are both likely to be able to make a comprehensive assessment. Surgical specialists are less likely to be consulted unless a surgically treatable problem comes to light. (One must bear in mind the original underlying spinal pathology present in the majority of cases).

Arachnoiditis does not present with a specific clinical picture of motor, sensory and reflex abnormalities: diagnosis tends to rest on further investigations such as MRI scans. There are, however, still some centres which perform myelograms as diagnostic procedures for arachnoiditis. Taking into consideration the fact that any foreign agent introduced into the spine has the potential to cause arachnoiditis, the rationale behind this type of testing seems questionable.

Burton ([571]) points out that whilst the incidence of arachnoiditis following non-ionic water-soluble myelographic agents is "quite small", if the "wrong water-soluble agents, or the wrong concentrations of agents, are administered there can be serious consequences such as permanent neurological injury or death." Moreover, he goes on to state "It is important to understand that myelography has never really been a great diagnostic study…a poor means of demonstrating many important entities such as pathology in the foraminal zone of the vertebral canal."

The current investigation of choice is a T2 weighted, fat suppressed, high-resolution MRI scan, including axial views. (Delamarter et al ([572]) suggested that T2-weighted images rendered the nerve root changes more visible than T1-weighted images.)

Ideally, a neuroradiologist experienced with the appearance of arachnoiditis should read the scan results. Whilst MRI scan CAN be used in patients who have 'hardware' in their spine (pedicle screws, plates, rods etc.), the presence of metal may cause significant image artefacts that make interpretation difficult. Titanium implants produce fewer artefacts.

MRI scans can be performed on patients with a 'pump' (intraspinal delivery of drugs). However, the scanner will temporarily halt the rotors of the pump.

MRI scans may not be possible in patients with a spinal cord stimulator.

MRI cannot be used in the following circumstances:

In patients with:

- A heart pacemaker
- A metallic foreign body in the eye
- Metallic vascular aneurysm clips
- A cochlear implant
- On life support systems which use ferromagnetic materials

Gadolinium has been used extensively to facilitate diagnosis of patients with Failed Back Surgery Syndrome, as it enhances scar tissue but not disc tissue, which therefore allows distinction to be made between recurrent disc herniation (treatable by surgery) and scar tissue (fibrosis), which tends not to be amenable to surgery.

However, more recently, more high-resolution scanning techniques have rendered the use of gadolinium less necessary for this purpose. 3D imaging allows for high resolution images in a reasonably short time sequence (other techniques may sacrifice resolution in a bid to achieve ultrafast MRI images.

A routine cervical spine MRI would include:

- Sagittal T1-weighted (T1W)
- Sagittal T2W
- Axial T2W

Routine lumbar spine MRI includes:

- Sagittal T1W
- Sagittal T2W
- Axial T1W and/or T2W

Simmons et al ([573]) note:

"It is critical when performing an MRI that a complete study be done. This includes sequential sagittal and axial high-resolution images to optimally evaluate all components of the spine."

Nelson recommends that MRI should include the thoracic region, as this may well be a site for constrictive arachnoiditis.

Massie et al. ([574]) gave a poster session at the 2001 Annual Meeting of the American Orthopaedic Research Society on the assessment of post-laminectomy scar formation. The goal of their animal study was to "correlate the histology results with MRI results and to show if the MRI can be used for assessing evidence of scar as new anti-inflammatory agents are approved for clinical trials." They found that there was a "pattern towards a correlation

between the MRI (with an injection of gadolinium) results and the histophomotery results." They therefore concluded that "The MRI can be a useful tool in assessing the presence and amount of scar", although they did remark that when the defect was small or there was minimal enhancement of the tissue between the osseous defect of the laminectomy site, that there was a discrepancy between MRI and histological findings.

ARACHNOIDITIS ON MRI

Nerve roots normally appear like strands of spaghetti, lying adjacent to each other, but in adhesive arachnoiditis the nerve roots are adherent to each other and thus distorted, resembling overcooked and matted spaghetti. This nerve root 'clumping' is one of the cardinal signs of arachnoiditis on radiographic images. As arachnoiditis progresses, the nerve roots are drawn out to the edge of the dural (thecal) sac, thereby producing an appearance known as the 'empty sac'. This may cause a 'string of pearls' appearance on axial views.

Various authors have described an intrathecal soft tissue mass (matted cauda equina) with a broad dural base which can cause obstruction to CSF flow. Focal or diffuse constriction and thickening of the thecal walls may also be noted.

Use of gadolinium contrast agent (see below) may show enhancement of thickened intradural (intrathecal) scar tissue.

Aldrete included the following arachnoiditis-related lesions that may be diagnosed by MRI scan:

- Nerve root clumping, unilaterally or bilaterally
- Adherence of nerve roots to the dural sac wall
- 'Empty sac'
- Arachnoid cyst with scarring
- Swelling or thickening of cauda equina
- Partial or complete obstruction of dural sac
- Compartmentalisation of dural sac
- Tethering of spinal cord
- Atrophy of spinal cord
- Filling defect of spinal cord
- Syrinx
- Subdural calcification

In terms of severity, Aldrete describes MRI findings as follows:

- **Absent:** normal distribution of nerve roots
- **Minimal:** 2 clumped nerve roots (unilateral) or thickened dural sheath

- **Mild:** 3-5 clumped roots, 1 or more adherent to dural sac
- **Moderate:** clumped nerve roots, bilateral, adhered to spinal cord, partial compartments within dural sac
- **Severe:** deformity of dural sac, pseudomeningocele, partial/complete obliteration
- **Extreme:** calcification of dural sac; pachymeningitis, nerve roots adherent to dura and/or cord, syringomyelia

Note:

False arachnoiditis: pseudo-clumping seen with spinal stenosis

Iophendylate residue may be seen as localised deposits, typically encapsulated and in some cases calcified (these may exert a localised mass effect) or as a thin film that resembles a layer of fat on either T1 or T2 images.

MRI in specific situations:

Intraspinal TB:

Gupta et al. ([575]) in India, looked at 20 patients. TB leptomeningitis was characterised by CSF loculation, nerve root thickening and clumping (in the lumbar region) or complete obliteration of the subarachnoid space. Gadolinium enhancement showed linear enhancement of the surface of the spinal cord and nerve roots or plaque-like enhancement of the dura-arachnoid complex. Intramedullary features included tuberculoma, cord oedema and cavitation.

Imaging Arachnoiditis Ossificans

Frizzell et al. ([576]) looked at MRI findings in arachnoiditis ossificans. They noted linear or mass-like intrathecal lesions with hypersensitivity on T1-weighted sequences and hyper- or hypo-intense on T2 weighted images within a setting of arachnoiditis. However, MR is limited in demonstrating small areas of calcification or ossification.

Faure et al. ([577]) stated: "MR imaging is a poor examination for this disease because it fails to show intracanal osseous formations."

Braz et al. ([578]) recently noted, "On MRI imaging the manifestations could be minimal and variable."

CT scan shows a typical picture depending on the type; a circumferential high-density structure following the contours of the spinal cord or cauda equina is path gnomonic of arachnoid ossification.

Revilla et al ([579]) described the ability of helical computed tomography (CT) in diagnosing calcified plaques; multiplanar reconstruction can be helpful in pinpointing location for the neurosurgeon's reference.

Arachnoid cysts:

Yu et al. ([580]) have studied arachnoid cysts using phase-contrast cine MRI that allowed them to measure brain motion and CSF flow during the cardiac cycle. They showed that brain motion was due to the volume difference between arterial and venous blood flow during a cardiac cycle, which thus drives CSF pulsation. Arachnoid cysts and subarachnoid space enlargement carried different curve patterns, thereby demonstrating that phase-contrast MRI and flow quantification can be a useful for non-invasive evaluation of brain motion and CSF flow and differentiation between arachnoid cysts and subarachnoid space enlargement.

Syringomyelia: MR features

Inoue et al. ([581]) looked at MRI features in 7 patients with syringomyelia associated with surgically proven spinal arachnoiditis, of which 5 were thoracic, 1 cervicothoracic and the remaining one extended from C4 to L1. All cases showed cord deformity due to adhesion or displacement due to an associated arachnoid cyst. This was best imaged on axial views. Flow voids could be seen in all cases on T2 weighted images.

How Useful is the MRI?

Kenneth Light, MD, a spine surgeon who has himself experienced severe back pain, has worked extensively with patients who have Failed Back Surgery Syndrome (i.e. have failed to get better after a back operation. He wrote in his article, "When the MRI lies" ([582]):

"It is up to the clinician, not the radiologist, nor the MRI scanner, to decide whether the anatomic lesion discovered by the test is clinically significant."

He concludes: "This test, like the myelogram and CT scan before it, is not a substitute for a careful history and physical examination."

One must also bear in mind that, as Deyo wrote in the New England Journal of Medicine ([583]) in 1994, "interpretation of MRI findings can vary substantially, so that the results may be equivocal despite the technique's aura of infallibility." Deyo goes on to comment:

"This variation...creates further opportunities for erroneous clinical decisions."

Sadly, at present, as Dr. Charles Burton of the Institute of Low Back and Neck Care in Minnesota remarks ([584]):

"most clinicians and radiologist are presently uninformed regarding quality studies and their interpretation", but, as he points out, this does not necessarily invalidate MRI scans themselves.

The NZHTA Report noted in its conclusions:

"Dependence on MRI or CT alone to detect abnormalities could result in inappropriate clinical evaluation and intervention."

It is important that treatable causes of Failed Back Surgery Syndrome (FBSS) such as recurrent disc herniation, disc fragments or spinal stenosis be excluded.

Functional MRI (fMRI) and PET scans have recently been developed: these are able to demonstrate the cerebral features of centralised pain.

New imaging techniques such as MTI may help in the future, as yet being untried with regard to arachnoiditis.

Ramli et al. reported recently ([585]) on a new imaging technique known as CISS (constructive interference in steady state), a type of MRI scan refinement. CISS is useful in "intraaxial and extraaxial cystic abnormalities, dysraphic malformations and disturbances of cerebrospinal fluid circulation, including post-traumatic and post-surgical scarring."

One must bear in mind that MRI demonstrates gross anatomical abnormalities, but cannot image physiological deficit, any more than a chest X-ray can show heart rhythm.

This brings us to **electromyography** (EMG) and **nerve conduction studies** (NCS). These tests are, of course, designed to elicit evidence of physiological impairment. However, as an undetectable level of nerve impairment can cause severe pain, these tests have limited value unless they are being used to assess the level of functional impairment.

The Guidelines for Clinical Practice and Facility Standards facilitated by the College of Physicians and Surgeons of Ontario in 2001([586]), clearly state:
"Studies may be falsely negative if they are performed either too early and/or too late in the course of radiculopathy. Electrodiagnostic studies cannot be used to "exclude" a radiculopathy. A clinically significant root lesion, particularly a chronic one, causing solely sensory complaints may be associated with a normal needle examination."..."Needle examination has a number of limitations. It assesses only motor fibres and detects primarily motor axonal loss."

The authors conclude: "Few studies have been done to assess evidence based medicine and specifically sensitivity and specificity as it relates to radiculopathy. Much of the evidence is based on experience and expert opinion."

Fibrescopes:
Warnke et al. ([587]) recently published the results of thecaloscopy performed on patients who had suspected arachnoiditis but no evidence on MR. The authors noted: "The 'gold standard' did not establish any treatable diagnosis in these patients." The results showed pathomorphological evidence of thickening of the arachnoid membrane in all the patients treated, and rootlets suggested by clinical examination were confirmed as showing signs of arachnoiditis. Isolated arachnoiditis was observed on single levels and one side. A further interesting finding was local raised CSF pressure that caused CSF to pour out under pressure during the procedure. They suggested that this is related to CSF circulatory disturbance, which may also dilate the thecal sac. Warnke also remarked on cases in which a 'large theca' was observed on MR, and the patients who experienced symptomatic relief after lumbar puncture due to temporary reduction in CSF pressure. "Thecaloscopy confirmed the suspected diagnosis in 100% of cases...we feel that the thecaloscope at least provides us with a safe diagnostic tool." In the 9 patients with arachnoiditis, there were no serious adverse events.

In September 2003, Tobita et al. ([588]) reported on the use of ultrafine flexible fibrescopes to view spinal epidural and subarachnoid spaces in patients with chronic pain. The authors assert, "Fine flexible fiberscopes make it possible to visualize the entire length of the spinal subarachnoid space without major complications." Their findings were: in 12 patients, new diagnoses were made, of which arachnoiditis 9, subarachnoid cyst 2, old subdural hematoma 1. MRI or CT had not detected these diagnoses. Additionally, chronic arachnoiditis was found in 2 patients with spinal trauma. Previously diagnosed pathologic changes were confirmed by fibrescopic examination in 16 patients of which arachnoiditis 11, spinal trauma 2, arteriovenous malformation 2 and subarachnoid cyst 1. The authors concluded: "These fine flexible fiberscopes may provide new diagnostic and interventional tools for spinal canal diseases, provided skilled techniques are applied."
Whilst minimally invasive, this type of investigation nevertheless carries a potential risk of exacerbating any existing arachnoiditis, although it may be of help in diagnosing the condition prior to proposed major invasive therapies (e.g. unavoidable spinal surgery), so that measures may be undertaken to minimize the negative impact of such treatment.

Thermography to image pain: Infrared thermal imaging (ITI) has a role in the assessment of neuropathic pain. Neurovascular autonomic tests have been performed in studies of patients with complex pain and ITI has been found to successfully differentiate between mechanical causes of back and neck pain and nerve-generated (neuropathic/neurogenic) pain. Hooshmand ([589]), an expert in Reflex Sympathetic Dystrophy (CRPS Type 1) has stated "ITI identifies hyperthermic foci of permanent sympathetic system damage sparing the patient from further damage by trauma of sympathetic nerve blocks." A significant number of arachnoiditis patients have features strongly suggestive of RSD-type damage and thus this test might be of help in ascertaining the source of their pain.

Lumbar puncture (LP): *(Invasive: NOT recommended);* in infective cases: chronic meningitis, which can be associated with arachnoiditis will show as: increased CSF pressure, possibly decreased glucose, increased protein, evidence of mononuclear cells. LP may be suggested if clinicians suspect Multiple Sclerosis.

Bladder dysfunction:
For bladder dysfunction, urological assessment and possibly urodynamic studies may be required. The Urodynamic test is designed to test the pressure in the bladder. In order to test the pressure a small catheter is inserted into the bladder. There is also a small rectal catheter and two small patches placed by the rectum. The bladder is then filled with water. When the bladder feels full, the patient urinates.
Cystometrogram (CMG) measures the bladder pressure as it fills, as well as testing bladder sensation, capacity and ability to expel urine.
Urethral pressure profile (UPP) measures the pressure along the length of the urethra as a catheter is being slowly removed. Uroflowometry (VFR) tests the force of the urine flow, measuring the amount and time taken voiding (into a special toilet)

Pressure flow study combines the CMG, VFR and electromyography (EMG). It measures both bladder pressure and urine flow. The EMG measures the activity of the pelvic floor muscles.
Multi-channel video urodynamics combine a pressure flow study with X-ray imaging of the bladder, to study the appearance of the bladder during filling, straining, coughing and voiding.
Post-voiding residual urine volume may be measured using ultrasound.

Urologists can also help to identify and treat sexual dysfunction. Gastroenterologists may be helpful in assessing bowel problems or difficulties in swallowing.

Clinical Investigations of AUTONOMIC dysfunction

By virtue of its many and complex functions, a complete assessment of the Autonomic Nervous System (ANS) is, of necessity, extremely complex. Cardiologists, gastroenterologists, urologists, and endocrinologists have used ANS testing most often, with neurologists and pain specialists only recently developing ways to evaluate patients with autonomic dysfunction.
The autonomic nervous system cannot be tested directly by conventional neurophysiologic techniques, i.e., nerve conduction studies and electromyography. The only way to assess function is indirect, by evaluating the response elicited reflexly by appropriate stimuli.
Until very recently, autonomic tests were available only in a few specialised centres.

Autonomic Reflex Screen (ARS)	
Tilt table test	Adrenergic vasomotor function
Deep breathing	Cardiovagal
Valsalva manoeuvre	Cardiovagal and adrenergic vasomotor
QSART	Postganglionic cholinergic sudomotor
CRPS Screen	
Temperature measurements	Index of sympathetic vasomotor tone
RSO*	Sudomotor and partially vasomotor
QSART*	Postganglionic sudomotor (stimulated)
TST	Thermoregulatory sudomotor pathways
*Performed simultaneously in bilateral, symmetrical sites.	

(Source: Testing the Autonomic Nervous System, Paola Sandroni, MD, PhD
IASP Newsletter, November/December 1998)

Investigations of pelvic pain

Perineal electrophysiological investigations (detection of neurogenic muscles of the perineal floor, increased sacral latency constitute: bulbocavernosus muscle EMG, measurements of bulbocavernosus reflex latencies (BCRLs) somatosensory evoked potentials of the pudendal nerve (SEPPNs) and pudendal nerve motor latencies (PNTMLs).

Cystometry and urethral pressure profile may be investigated if there are urinary symptoms.
Note: "the presence of pudendal neuralgia should prompt a search for an underlying cause, and that this severe neuropathic pain syndrome is effectively managed with adjuvant analgesics." ([590]) In the Canadian study, 6 patients with pudendal neuralgia all had diabetes and/or neoplastic conditions.

NOTE: 25 percent of lumbosacral plexopathies are metastatic ([591]). Pain is usually felt in the lower abdomen, buttock, and leg. Infiltration of the sacral plexus may produce perineal and perirectal pain, which is exacerbated by sitting and lying prone. Pain typically precedes, by weeks or even months, the neurological signs of weakness, sensory loss, or urinary incontinence. Abdominal and pelvic CT or MRI may provide the diagnosis. MRI of the epidural space is also required to exclude epidural disease of the cauda equine or leptomeningeal mass which may produce a clinical syndrome similar to lumbosacral plexopathy ([592]).

ASSESSMENT: OF OSTEOPOROSIS
Osteoporosis risk-factor questionnaire
DEXA study (radio-imaging with low radiation): bone scan of spine, hip and wrist checks bone mineral density.
If there are osteophytes (bony spurs) and/or crush fracture, then an X-ray is also required. Note that X-ray alone only detects 30% or greater bone density loss.
Risk of fracture may be assessed using a Quantitative Ultrasound (QUS)

Investigations for Hydrocephalus:
CT, MRI, Lumbar Puncture, Intracranial pressure (ICP) monitoring, measurement of CSF outflow resistance, and topic Cisternography.

Psychological assessment:
Chronic, intractable conditions such as arachnoiditis present the sufferers with a wide range of challenges day by day; in addition to the physical effects, it is important to acknowledge the inevitable psychological toll of unremitting pain and loss of function.
Haythornthwaite and Benrud-Larson ([593]) reviewed studies on the psychological assessment and treatment of neuropathic pain conditions, including postherpetic neuralgia (PHN), diabetic neuropathy, complex regional pain syndrome, post spinal cord injury, post amputation, and AIDS-related neuropathy. They noted: "the assessment of neuropathic pain needs to include measurement of multiple dimensions of quality of life." They included mood, physical and social functioning, and pain-coping strategies as important aspects of the patient's overall wellbeing.

TREATMENT OPTIONS

Generally speaking, **this complex neurogenic pain syndrome is best treated at a specialist pain clinic, with a multidisciplinary approach.**

As yet, a curative treatment is unavailable, so management revolves around palliative care principles.

AIMS IN MANAGING ARACHNOIDITIS

The goal of chronic pain management is always to reduce pain (not to eliminate the pain completely) and improve the person's ability to cope with the pain that remains.
Other aims include:

- Greater endurance
- Increased strength
- Improved flexibility
- Improved functioning at home
- Improved interaction with family and friends: reduced isolation
- Improved overall quality of life
- Return to employment if possible
- Optimised / Decreased medication use (reduced side effect profile)
- Fewer visits to doctors
- Fewer hospitalisations and emergency department visits
- Lower costs of maintaining pain care

There should be 3 major components to arachnoiditis treatment:

1. **Management of symptoms**
2. **Prevention of secondary and tertiary problems**
3. **Minimisation of ongoing pathology (and avoidance of trigger factors for exacerbation)**

SURVEY RESULTS:

In the Global survey, only 3% of respondents were not using medication regularly. In the New Zealand survey, the figure was 20%. In the latter, 12% found no treatment effective, 24% were on drug therapy alone, 44% were on drugs and other treatments, and 20% were only on non-pharmacological treatments. Those on medication were on between 1 and 7 different drugs.

The predominant pain is as we have seen, neuropathic, so that regimes should be based on this.
Sindrup and Jensen ([594]) reported on treatment of polyneuropathy in 2000: they stated NNT's* for the various treatments as follows (based on placebo-controlled trials and calculated numbers needed to treat (NNT) to obtain one patient with more than 50% pain relief): *NNTs (Number Needed to Treat) are figures representing how effective a treatment is: low= more effective

- Tricyclic antidepressants: 2.6
- Selective serotonin reuptake inhibitors: 6.7
- Anticonvulsants sodium channel blockers: 2.5
- Anticonvulsant calcium channel blocker gabapentin: 4.1
- Tramadol (mixed opioid and monoaminergic drug): 3.4
- Dextromethorphan (NMDA-antagonist) 1.9
- L-dopa: 3.4
- Capsaicin: 5.9 (note: data are controversial owing to trial methodology)
- Mexiletine: 38 (biased because of a lack of dichotomous data in several positive trials)

The New Zealand survey ([595]) found:

In terms of the success of different types of treatment:

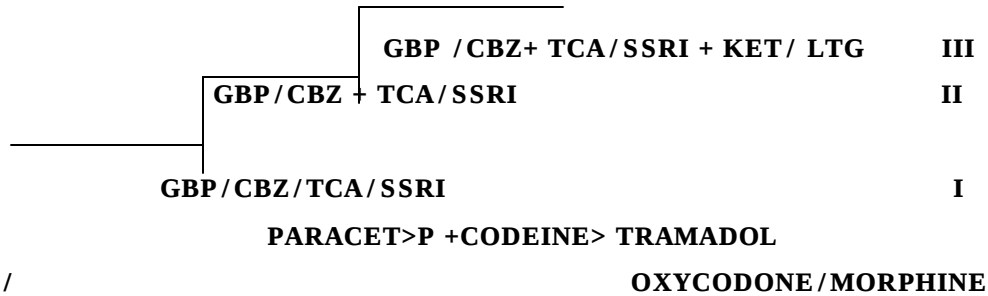
12% found that no treatment helped. 24% found relief solely from drug treatment, whilst 44% improved with drug and 'other treatment' (by contrast, of those using 'other treatment' but no drugs only 20% had relief.)

68% of the respondents were using drugs (58% narcotic; 15% anti-inflammatory; 11% anticonvulsant; 18% antidepressant; 17% muscle relaxant).

A variety of other measures were being used by the respondents to reduce their pain: rest, warmth, massage, TENS, acupuncture, relaxation/self hypnosis, frequent position changes etc.

Current treatment practice using a neuropathic pain ladder similar to the WHO pain ladder would suggest the following strategies:

NEUROPATHIC PAIN LADDER (after Nurmikko)



Key: GBP= gabapentin (Neurontin); CBZ= Carbamazepine (Tegretol); TCA= tricyclic antidepressant (e.g. Amitriptyline, Nortriptyline); SSRI= Selective Serotonin Reuptake Inhibitor (e.g. Paroxetine, Fluoxetine)

KET= sublingual ketamine; LTG= Lamotrigine

PARACET (P)= paracetamol

Major sensory loss due to deafferentation may best be treated using lamotrigine or topiramate as they have multiple actions.

Devulder and Crombez ([596]), in writing about central pain, suggest that "amitriptyline as an adrenergic reuptake inhibitor and the sodium channel blockers are the drugs of first-choice". Advanced treatment might require a test procedure with lignocaine, propofol or ketamine.

Opiates

Of the well-established treatment regimes, **opiates** are frequently used. However, these may be ineffective in combating any central component of the pain.

Survey findings on opiate use: New Zealand survey: 58%, Global 56%, and Long 71%

The issue of addiction and dependency concerns most practitioners and may lead to reluctance to prescribe. There will most certainly be physical dependence, and the problem of withdrawal symptoms if the opiate medication is discontinued. Also, there is an element of tolerance that may develop in long-term use, with the need for increasing doses for effective pain relief. This is not a major problem in most patients. Addiction - psychological dependence and abuse - is very unusual in chronic pain patients treated with an appropriate level of analgesia, as opposed to those who use opiate drugs for recreational purposes (see Side Effects).

Note that, unlike anti-inflammatory drugs (NSAIDs), opiates do not cause damage to organs.

It is best to start with short-acting morphine such as Oramorph, 4- hourly, until adequate analgesia is established. Breakthrough pain may require top-up doses. Once control has been established, it is advisable to change to a slow release preparation such as MS Continus or Oramorph SR, which has a predictable duration of action for 8-12 hours, and can thus be given twice daily. Oxycodone is a new preparation now being prescribed.

One of the most important points that patients need to be made aware of is the need for 'round the clock' dosing rather than in response to pain (prn, as required). This approach achieves a much better pain relief, whilst minimising side effects. Fluctuations in dose requirement may occur, and in this case, the slow-release preparation should be replaced with a shorter acting one for the period of increased dose requirement.

Patients also need to be aware that the initial side effects of nausea and sedation are transient and should subside within two weeks or so, as tolerance to these effects develops. The most persistent side effect is constipation (see below).

Occasionally opiates may induce a paradoxical hyperpathia, (increase in pain) which is resolved by substitution with an alternative opiate medication. ([597])

Morphine medication is available in many preparations including:

Sevredol® IR; Oramorph IR;; Morcap ® SR 20mg/12hr. or 40mg/24hr. ; MXL® sustained release 30/60/90/120/150/200mg;

Oxycodone: Oxynorm ® (ONR start 5mg 4-6 hourly) Oxycontin (oxycodone SR)

IR= immediate release; SR= slow release

Other opiates include:

Methadone: which can be beneficial for neuropathic pain, but may have an unpredictable duration of action

Pethidine has unwanted central effects and is too short acting

Dextropropoxyphene: a weak agonist, possibly metabolised to a cardiotoxic metabolite. (a recent paper ([598]) has described it as an NMDA antagonist: see below) available in **Co-proxamol/ Distalgesic** (32.5mg combined with 325mg paracetamol) or **Doloxene** (60mg)

Fentanyl: Short acting: lozenge form helpful for incident pain: patch helpful for background analgesia;

Pentazocine (Fortral®)

Palfium® dextromoramide

Palladone ® hydromorphone

Remedeine® paracetamol + dihydrocodeine

Dihydrocodeine

There are also partial opiate agonists such as buprenorphine (**Temgesic**®), which has a maximum analgesic dose equivalent to moderate doses of narcotics, but tend to cause less dependency. It has been used sublingually for some time (200-400 microgrammes 6-8 hourly).

Recently a buprenorphine patch (Transtec®) has been licensed for use in chronic severe non-malignant pain. The patch can replace weak or strong opioids or be used in combination with other analgesic agents if required. The starting dose in opioid naïve patients is 35 microgrammes/hour; patch is applied every 3 days.

In March 2003, an article was published in the prestigious New England Journal of Medicine ([599]), which reported on a randomised study of the mu agonist **levorphanol**. 81 adults with refractory neuropathic pain received either high dose (0.75mg) or low dose (0.15mg) capsules of levorphanol increased as individuals' requirements necessitated up to a maximum of 21 capsules a day. In the high dose study, 66% of the patients who completed the study had moderate or better pain relief. Examination may or may not reveal significant neurological deficit. However, the possibility of pain of central origin should be borne in mind even if there is no obvious clinically observable abnormality.

The presence of central sensitisation will confer poorly localised pain that does not conform to dermatomal distribution. It is likely to be dysaesthetic pain that is difficult for the patient to describe.

Dropouts from the study were due to side effects. In addition to pain relief, there were improvements in mood, function and sleep. The authors concluded that levorphanol is as effective as tricyclic

antidepressants and gabapentin, but that there may be intolerable side effects. In an accompanying editorial, Dr. Kathleen Foley of the Memorial Sloan-Kettering Cancer Center in New York noted that the study supports the concept of opioid responsiveness in neuropathic pain syndromes, although it fails to address longer-term efficacy. She suggested an individually- tailored approach bearing in mind the possibility of rotating various opioids to maximise analgesia and minimise adverse effects.

Note: special precautions need to be taken with some opiates in hypothyroidism, hepatic/renal impairment, raised intracranial pressure, biliary tract disease (gallbladder etc.), pancreatitis, prostatic hypertrophy (enlarged prostate> may lead to urinary retention). Opiates tend to interact with other medication in particular CNS depressants, MAOI antidepressants, and some preparations may affect antihypertensives (blood pressure tablets), muscle relaxants, quinidine, erythromycin, cimetidine and ketoconazole.
ADRs: (adverse drug reactions) with opiates include: nausea, somnolence (usually subsides after 1-2 weeks) constipation, blurred vision, fluid retention, confusion, itching/skin flushing. Fentanyl patch can also cause skin reaction; drop in blood pressure, hallucinations, hypoventilation (reduced breathing rate), bradycardia (slow pulse), sweating, euphoria and headache.

Treatment of breakthrough pain (see also below)
McQuay ([600]) describes **incident pain**, which may be brought on by activity, and is a major problem, as adequate background analgesia may be insufficient to control it. There may also be another type of incident pain, which is intermittent, and can occur at rest, without obvious trigger factors. It is very difficult to control. Use of the fentanyl lozenge (Actiq ®) may be useful in this situation. OTFC delivers fentanyl within a sweetened matrix that dissolves in the mouth. The fentanyl is absorbed rapidly through the buccal mucosa due to its high lipid solubility.

A recent Reuters Medical News bulletin (November 29, 2002), reports on a study of 100 patients with severe chronic non-malignant pain (duration at least 3 years), treated with oral transmucosal fentanyl citrate (OTFC). More than half the patients suffered from degenerative spine disease, some had neuropathy, migraine etc. and all were being treated with both a long-acting opioid and a short-acting one for breakthrough pain. Patients used OTFC for severe breakthrough pain, and were able to reduce or eliminate use of the short-acting opioid by replacing it with OTFC. Pain relief was reported within 10 minutes of using OTFC. Almost 3 quarters reported relief lasting at least 2 hours and more than 1 quarter found it lasted more than 4 hours. 62% reported fewer days confined to house or bed, 50% required less opioid medication and experienced less depression and anxiety and 45% were sleeping better. Side effects of constipation, itching and nausea were reduced, as was headache. The study was published in the October issue of the American Journal of Pain.
Coluzzi et al. ([601]) compared the efficacy of OTFC with that of immediate release morphine (MSIR) and found that OTFC gave significantly better outcomes relating to pain intensity and relief. Common side effects

include somnolence, nausea, constipation and dizziness; a long-term safety study ([602]) in cancer patients, OTFC was not found to be associated with any additional side effects.

Cephalon UK has recently (9th.April 2003) recalled batches of Actiq that had been distributed in the UK, as a precautionary measure to avoid any risk of overdose of fentanyl in patients, which in extreme cases could be fatal. During testing they found that a very small number of the lozenges had an amount of fentanyl higher than it should be. Although the number of lozenges that seemed to be affected was very low, Cephalon felt it was important to recall the supplies in order to avoid any patients taking an affected lozenge. Anyone taking an affected lozenge might experience:

? Excessive sleepiness (hypersomnolence)
?Low/shallow breathing (hypoventilation)
?A slowing of your pulse/heart rate (bradycardia)
?Dizziness (hypotension)

Cephalon routinely issue the following warnings with their product in the USA:

> Indicated only for the management of breakthrough cancer pain in patients with malignancies who are *already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain*.
> Because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates, ACTIQ is contraindicated in the management of acute or postoperative pain.
> This product *must not* be used in opioid nontolerant patients.
> Patients considered opioid tolerant are those who are taking at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.
> Patients and their caregivers must be instructed that ACTIQ contains a medicine in an amount, which can be fatal to a child. Patients and their caregivers must be instructed to keep both used and unused dosage units out of the reach of children and to discard opened units properly.
> While all units should be disposed of immediately after use, partially consumed units represent a special risk because they are no longer protected by the child-resistant pouch, yet may contain enough medicine to be fatal to a child.
> ACTIQ is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.
> The most common side effects observed in ACTIQ clinical trials were somnolence, nausea, vomiting, and dizziness.
> Patients should be closely followed and the dosage level changed until the patient reaches a dose that provides adequate analgesia using a single ACTIQ dosing unit.
> Once a successful dose has been found, the patient should limit consumption to four or fewer units per day.

<u>New Developments:</u>

Currently nasal preparations of morphine are in development. One formulation uses chitosan, in order to increase the time the preparation remains on the nasal mucosa, thereby increasing bioavailability. A small trial of 14 patients ([603]) demonstrated that it was effective with a rapid onset within 5 minutes. Intranasal fentanyl has been used in 12 cancer patients ([604]) and found to give relief within a few minutes, with 7 patients reporting reduced pain after 10 minutes. Further trials are necessary. Dale et al. ([605]) reviewed nasal administration of opioid drugs, including studies in volunteers using fentanyl, alfentanil, sufentanil, butorphanol, oxycodone and buprenorphine. Fentanyl, pethidine and butorphanol have been studied for postoperative pain. Onset times range from 12 -22 minutes and times to peak effect from 24- 60 minutes, with considerable interindividual variation. The authors concluded: "Nasal administration of opioids has promising features, but is still in its infancy."

Combination preparations:

MorphiDex® is a combination drug developed by Algos. This drug combines the NMDA receptor antagonist dextromethorphan with morphine, thereby increasing the effectiveness of the narcotic without increasing side effects. Preclinical and double-blind single-dose placebo-controlled studies demonstrated that MorphiDex (MS: DM), a 1:1 ratio of morphine sulphate (MS) to dextromethorphan hydrobromide (DM), provides significantly greater analgesia than an equal dose of immediate release MS, with a faster onset, and a duration of 8 hours or more. ([606])

Equagesic® = ethoheptazine cit.; meprobamate 75mg, aspirin 250mg, for use short-term for musculoskeletal pain.

Tramadol (**Tramal/Ultram/Zydol/Zamadol®**) is a synthetic centrally acting analgesic, which is unrelated to opiates and carries less risk of dependence. It is a weak noradrenaline inhibitor and serotonin inhibitor and has weak opioid effects. It is useful for moderate to severe pain and has few serious side effects. Harati et al. ([607]) found in a double blind, controlled trial of 131 patients with painful diabetic neuropathy, that there was a significant reduction in pain intensity at week 6. There was a 15% dropout due to adverse events.

However, it should be used with caution in patients who are also taking CNS depressants. Tramake ® is tramadol in sachet form, to be taken 50-100mg every 4-6 hours. Hummel et al([608]) have suggested that tramadol (like dihydrocodeine which they also studied) may exert a stronger analgesic effect when administered in the evening, and they recommend taking this into account if the usual routine of prescription leads to either an increase of pain in the morning (due to insufficient analgesia) or unnecessary excessive dose in the evening. A slow-release preparation is available and can be given twice a day. (Every 12 hours) and this may circumvent these problems. Indeed, as neuropathic pain is often worse at night, if there is a greater analgesic effect in the evening, this may be beneficial when used for this purpose.

Antidepressants.

The clinical "bottom line" (Source: Bandolier [609]): antidepressants are effective in reducing neuropathic pain. The overall NNT (number needed to treat) for at least 50% pain relief compared with placebo is 3 (2.4-4) : 30% of patients will gain more than 50% relief, 30% will have minor adverse reactions and 4% will need to stop treatment because of major adverse reactions. SSRIs may be less effective but carry a 50% reduction in major adverse effects.

NNH (number needed to harm) for minor adverse effects is 3.7 (2.9- 5.2) across various pain conditions. NNH for major adverse effects is 22, although they were lower for SSRIs than for tricyclic antidepressants.

Amitriptyline (Lentizol®), a Tricyclic Antidepressant (TCA), is viewed by many as the agent of choice, because experience with it has been most widely reported. Generally, it is used to treat neuropathic pain at doses much lower than those used to combat depression. Beneficial effects on pain may begin after about

ten days (compared with about three weeks for antidepressant action). It produces anticholinergic side effects such as dry mouth, constipation, blurred vision and urinary retention. Dry mouth and drowsiness are experienced by about a third of patients. Amitriptyline is popular among Central Pain patients, not only because it makes dysaesthetic burning on the skin more bearable, but also because it lessens the hyperpathic pain of bladder distension.

Clomipramine (Anafranil®) is a tricyclic antidepressant that also has SSRI properties.
SSRIs: This type of antidepressant is much less effective in the treatment of neuropathic pain. Some clinicians state that SSRIs are virtually useless, unless there is an element of depression as well as pain. SSRIs like **Prozac** tend to be less effective in treating pain although they have fewer (paroxetine) or no (fluoxetine, sertraline, fluvoxamine) anticholinergic effects.
The commonest side-effect is gastrointestinal distress (nausea, vomiting, diarrhoea), occurring in 20-40% of patients. SSRIs may carry other unpleasant side effects especially initially when they may cause agitation, distress and disturbed sleep. Sexual dysfunction of various types occurs in approximately 20-40% of patients on SSRIs (reports as high as 75% have resulted from direct interviews).

The double-blind, placebo-controlled, cross-over clinical trial by Max et al.([610]) in 1992, on patients with painful diabetic neuropathy, published in the *New England Journal of Medicine*, compared the efficacy of a tertiary amine, amitriptyline, to that of a secondary amine, desipramine, and the selective serotonin reuptake inhibitor (SSRI), fluoxetine. The doses were about 100 mg each for amitriptyline and desipramine, and 40 mg for fluoxetine. It was found that while on amitriptyline, 74% of patients experienced moderate or significant pain relief compared to 61% while on desipramine and 48% while on fluoxetine. Note that 41% of placebo-treated patients also had moderate or significant pain relief, which means that the SSRI barely outperformed placebo.

Seroxat: there has been considerable controversy of late over this SSRI drug (Paroxetine). Whilst it undoubtedly helps great numbers of depressed patients, there have been various reports about the adverse effects, including what has been described as 'mental turmoil' (daytime irritability, morose and even suicidal thoughts, bizarre nightmares) and uncharacteristically violent behaviour (towards the self and/or others). These can occur on starting the drug, within a few doses. They could be attributable to the initial decrease in serotonin that the drug causes. In addition, people have had difficulty stopping the drug. Although the manufacturers and many doctors fail to recognise the problems, there is a well documented set of withdrawal symptoms, including unpleasant experiences such as electric shock type sensations.

Dual reuptake agents such as tricyclic antidepressants (TCAs), venlafaxine (at doses of 150 mg/day or higher), mirtazapine, and monoamine oxidase inhibitors appear to be more effective than selective serotonin reuptake inhibitors (SSRIs) alone in treating either pain or depression. In one large meta-analysis, venlafaxine at daily doses of 150 mg or greater was associated with higher remission rates than SSRIs (45% vs. 35%, respectively).

Mattia et al. ([611]) reviewed new antidepressants for treatment of neuropathic pain. They discussed three classified categories: Serotonin and Noradrenergic Reuptake Inhibitors (SNaRI), such as venlafaxine and nefazodone; Noradrenergic and Specific Serotoninergic Antidepressants (NaSSA), e.g. mirtazapine, and Noradrenaline Reuptake Inhibitors (NaRI), such as reboxetine. They noted that Venlafaxine (SNaRI), the most investigated of these new drugs, has been shown to be effective in the treatment of different kinds of pain, and has a significantly better side-effects profile than TCAs.

In Israel, a recent study looked at the antinociceptive properties of venlafaxine and mirtazapine. ([612]) Venlafaxine is a drug that blocks the synaptosomal uptake of noradrenaline and serotonin and, to a lesser degree, of dopamine and mirtazapine enhances noradrenergic and 5-HT1A-mediated serotonergic neurotransmission. It was found that both drugs have an effect on opioid receptors.

The antinociceptive effect of venlafaxine is influenced by opioid receptor subtypes (mu-, kappa1- kappa3- and delta-opioid receptor subtypes) combined with the alpha2-adrenergic receptor, whereas the antinociceptive effect of mirtazapine mainly involves mu- and kappa3-opioid mechanisms. The authors Schreiber, Bleich and Pick suggested "This opioid profile of the two drugs may be one of the explanations to their efficacy in severe depression, unlike the SSRIs and other antidepressants which lack opioid activity." The same could be said of their efficacy in treating pain. Schreiber et al. ([613]) concluded that the antinociceptive effect of mirtazapine is mainly influenced by the kappa (3)-opioid receptor subtype combined with both serotonergic and noradrenergic receptors. The authors stated: "These results suggest a potential use of mirtazapine in the management of some pain syndromes". They did, however, point out: "However, further research is needed in order to establish both the exact clinical indications and the effective doses of mirtazapine when prescribed for pain."

Theobald et al. ([614]) conducted a pilot study on mirtazapine in cancer patients. They found trend level differences for pain, pain relief, and mood and on numeric rating scales measuring nausea, anxiety, insomnia, and appetite. The authors concluded, "This open-label pilot study suggests that mirtazapine may be effective for improving multiple symptoms, depression and quality of life in patients with advanced cancer".

Finnish authors, Tasmuth, Hartel and Kalso, ([615]) conducted a randomised controlled trial of venlafaxine for neuropathic pain following treatment of breast cancer. They found that the average pain relief (diary) and the maximum pain intensity (retrospective assessment by the computer program) were significantly lower with venlafaxine compared with placebo. Poor responders had low venlafaxine concentrations whereas those with high venlafaxine concentrations had "excellent pain relief". They concluded that higher doses could be used in order to improve pain relief.

A recent Danish study ([616]) showed that venlafaxine successfully reduced pain paroxysms, constant pain, and pressure-evoked pain in neuropathy (although, like other agents, was ineffective against touch-evoked pain). The authors of the study concluded: "Venlafaxine relieves pain in polyneuropathy and may be as effective as imipramine."

Briley ([617]) wrote favourably about agents such as venlafaxine, milnacipran and duloxetine, suggesting: "these compounds may be effective in relieving pain both associated with, and independent of depression."

The Danish University Antidepressant Group found similar results when comparing citalopram and paroxetine with clomipramine.[15]

Note: Drug Interactions: Antidepressants such as TCAs are central nervous system depressants and may interact with other CNS depressants such as opiates (morphine etc.) or benzodiazepines and increase sedation and possibly respiratory depression.
Either SSRIs or TCAs, if given with tramadol may increase the risk of seizures. Paralytic ileus (gut motion stopped) may occur in patients taking TCAs in combination with anticholinergic drugs such as oxybutinin (used for bladder dysfunction). Anticonvulsant drugs may lower the plasma concentration of antidepressants. TCAs may enhance the muscle relaxant effect of baclofen.

Antidepressants are also helpful in tackling urinary incontinence if the bladder muscle is hyperactive (detrusor instability). Conversely, if there is a tendency for the bladder not to empty efficiently or there is some degree of urinary retention these drugs are not suitable as they may exacerbate the problem or even cause full-blown urinary retention, requiring catheterisation.

Buproprion (Wellbutrin): a study by researchers at the University of Arizona ([618]) and funded partly by the manufacturers, has found that 71 percent of patients with neuropathic pain reported that their pain decreased on Bupropion, and only suffered mild side effects such as dry mouth, insomnia and headache. The authors concluded: "bupropion SR* (150-300 mg daily) was effective and well tolerated for the treatment of neuropathic pain." * SR=Slow release

Other neurotransmitters may be involved. Descending modulatory pathways mediated by serotonin, norepinephrine, and gamma amino butyric acid may be used to limit the intensity of pain signals arriving in the brain from the body via spinal pathways. Disruptions in this pathway or in the limbic system (controlling mood) may have the ability to influence or even disrupt the other. Although speculative, this may account for the numbers of patients developing depression in response to chronic pain or for depression acting as a "soil" for the development of chronic pain states in patients with known vulnerability to mood disorders.

Other theories of interaction have also been suggested. One such theory emphasizes dysregulations in the hypothalamic-pituitary-adrenal (HPA) axis and reductions in brain-derived neurotrophic factor (BDNF). Changes in BDNF in depressed patients are the subject of current research. BDNF levels in the hippocampus are reduced by increased levels of endogenous glucocorticoids often seen in depressed patients. BDNF appears to retard neuronal atrophy under stress, and a loss of such protection may inhibit

accommodation and response to stress that involves both neuron preservation and neurogenesis. Antidepressants may increase levels of BDNF as a key part of their mechanism of action.

Anticonvulsants

Anticonvulsants such as carbamazepine are particularly useful for the sharp, lancinating type of neuropathic pain.

Carbamazepine (Tegretol®) was the first of this class of drugs to be studied in clinical trials and has been longest in use for treatment of neuropathic pain. Its use in treating trigeminal neuralgia has been established in clinical trials, but data for use in diabetic neuropathy is less convincing. 70 to 90% of patients with trigeminal neuralgia experience a good initial response to this drug. Indeed, experts in this field suggest that a failure to respond to CBZ suggests an incorrect diagnosis.

On a dose of 200mg twice a day, within 1-2 days the pain is significantly relieved. Once autoinduction occurs, the dose may need to be increased to 600-1000mg daily. There is a good correlation between efficacy and serum drug levels, the effective serum level range being 6-10mg/cc, usually achieved on daily doses of 400-1000mg.

However, at follow-up to there is about a 30 to 40% drop-out rate at 1 year, either because of the development of tolerance or because of the development of significant side effects.

Carbamazepine has significant side effects, including nausea/vomiting; diarrhoea; rash, pruritus (itching); fluid retention (low sodium); drowsiness, dizziness, blurred vision, lethargy, headache, tinnitus, paraesthesia (tingling), abnormal involuntary movements, leg cramps. Urinary frequency or occasionally acute urinary retention may occur. It also has numerous drug interactions, including calcium channel blockers e.g. Nifedipine; Verapamil (may be used to treat high blood pressure); Digitoxin (for abnormal heart rhythm), corticosteroids, diuretics ("water tablets" for fluid retention) Danazol (hormone), oral contraceptives, Lithium, muscle relaxants, Theophylline (used to treat asthma), Thyroxine, Cimetidine (ulcer-healing) Fluoxetine (Prozac), Erythromycin (antibiotic).

Liver enzymes and haematological indices should be monitored.

Oxcarbazepine: is a keto-analog of carbamazepine can be given twice daily and there is no autoinduction. It has a low propensity for drug interactions and fewer side effects than CBZ, whilst being as effective for pain relief. In epilepsy trials, it has been better tolerated than CBZ. Oxcarbazepine is new in the United States, but has been approved in more than 50 countries.

In trigeminal neuralgia, oxcarbazepine (OXC) has been tested in a number of clinical trials. Lindstrom ([619]) performed a comparative trial of OXC vs. CBZ in a cross-over design. OXC was titrated to 900-2100 mg/day vs. CBZ at 400-1200 mg/day. The efficacy was assessed on an 11-point scale and the data showed comparable analgesic effect in 12 patients, better efficacy on OXC for 2 patients and better efficacy for CBZ in 1 patient. The author concluded that OXC offers an alternative to CBZ for the treatment of trigeminal neuralgia. With regard to dosage, 1mg CBZ is equivalent to 1.5mg OXC. Remillard ([620]) looked at use of OXC to treat trigeminal neuralgia refractory to CBZ treatment. 67% of the 15 patients were completely

controlled on 900-1800mg/day and a further 20% were controlled with occasional exacerbations on doses of more than 2g a day.
Beydoun et al. presented findings of 3 double-blind randomised studies of OXC versus CBZ at the American Pain Society Meeting in 2002. In newly diagnosed trigeminal neuralgia, 48 patients on 750mg OXC or 500mg CBZ median dose and 2 studies of refractory trigeminal neuralgia (84 patients) at 1050-1200mg OXC daily and 700-900mg CBZ showed that OXC has a similar efficacy to CBZ but fewer side effects.
Carrazana et al. presented at the same meeting, findings from a study of the use of OXC in painful diabetic neuropathy. 50% of patients experienced a 50% of better improvement in VAS scores, and both primary and secondary variables on the Quality of Life questionnaire improved.

Neurontin (gabapentin) is useful for pain relief and muscle spasms. It has been demonstrated as helpful in diabetic neuropathy and post-herpetic neuralgia. Recent studies have also shown that it is beneficial in post-amputation pain ([621]) and also in patients with spinal cord injury. In the SCI study ([622]), there was a "significant decrease of "unpleasant feeling" and a trend toward a decrease in both the "pain intensity" and "burning sensation" at the fourth week of gabapentin treatment compared with those on the placebo."

A recent randomised, double-blind study in Glasgow ([623]) found that Gabapentin was effective in a range of conditions causing neuropathic pain, including features of allodynia and hyperalgesia.
A Finnish group published a paper in October 2002 ([624]), in which they looked at the use of anticonvulsants in central pain. The authors concluded: "Present suggestions for anticonvulsant treatment of CP are lamotrigine as the first choice, followed by gabapentin or carbamazepine/oxcarbazepine. These compounds are considered as effective as the antidepressant amitriptyline."

In November 2002, Hurley et al ([625]) reported on animal studies, which showed that gabapentin (and pregabalin: see below) interacts synergistically with the NSAID Naproxen to reduce hyperalgesia. The authors suggest that low dose combinations may be effective for persistent inflammatory pain.
It is important to start at a low dose (300mg at night) and increase very gradually to reduce the impact of side effects, which include sleepiness and unsteady gait. Some people report weight gain and others experience clouded thinking abilities on this drug. Usually a dose of around 2400mg a day is helpful in combating nerve pain.

Note that Gabapentin interacts with antacid medication, but not other drugs (this is one of its advantages.)

ADRs listed in MIMMS include: somnolence, dizziness, ataxia, fatigue, tremor, nystagmus (flickering eyes), diplopia (double vision), dysarthria (difficulty talking), amnesia, joint pains, purpura (rash), GI upset, anxiety, weight gain, urinary tract infection and pharyngitis.

Other anticonvulsants include: **Lamotrigine**, which has been reported to be effective in relieving pain from trigeminal neuralgia refractory to other treatments, HIV neuropathy, and central post-stroke pain.

Zonisamide may be effective in controlling neuropathic pain symptoms. Other anticonvulsants, including lorazepam, valproate, topiramate, and tiagabine, have also been under investigation.
There are no double-blind trials of the other anticonvulsants. The data for phenytoin suggest that high dosages and high serum levels between 15-25 mg/cc facilitate a positive response in a proportion of patients; mostly it has been mostly used as an adjuvant to CBZ in patients with only a partial response to this drug.
With clonazepam, there have been 2 open-label series, of 25 and 19 patients, of which approximately two-thirds of the patients were reported to have a positive response. A single open-label series of 20 patients taking valproate showed that about half experienced a positive response.

Novel Anticonvulsant, **Pregabalin** is a second-generation anticonvulsant agent similar to gabapentin but about 6-fold more potent. In animal studies, pregabalin has been found to be effective in raising the pain threshold, reducing allodynia, increasing slow-wave non rapid eye movement (REM) sleep, relieving anxiety, modulating acute pain symptoms, and reducing colon-related pain.([626]- [627]) However, it may also induce nocturnal myoclonus.([628])
An 8-week, multicentre, randomised, double-blind, placebo-controlled study by Crofford et al ([629]) from the University of Michigan, Arbor and colleagues from several other institutions evaluated the efficacy and safety of pregabalin in patients with Fibromyalgia (FMS). Patients treated with the highest dose, 450 mg/day, of pregabalin experienced significant improvement in the end point mean pain score compared with those receiving placebo, and were more likely to experience a 50% reduction in pain. For patients receiving either 300 or 450 mg/day, other variables, such as the mean sleep quality, fatigue were improved significantly. Patients in all treatment groups demonstrated significantly improved Sleep Index scores In total, 9% of patients withdrew from the study because of adverse side effects (most commonly dizziness and somnolence) and 8% because of poor efficacy.
The other newer anticonvulsant felbamate was tested in 3 patients with refractory trigeminal neuralgia who had a good response. Unfortunately the drug is associated with significant idiosyncratic reactions including aplastic anaemia and fulminant hepatic failure, which renders it unlikely to be further developed as a treatment for neuropathic pain.
Topiramate has not been found to be statistically effective relative to placebo in three large randomised multi-centre trials, so there is no evidence-based data to support its use in neuropathic pain. It causes significant side effects including weight loss.

NMDA RECEPTOR ANTAGONISTS

Dextromethorphan: available OTC as a cough suppressant, it is a low-affinity NMDA receptor antagonist; it is rapidly metabolised to dextrorphan, which is an active metabolite that also has NMDA receptor

activity. Various studies have had mixed results, but Nelson's study ([630]) of dextromethorphan in diabetic neuropathy and post-herpetic neuralgia (using an initial dose of 120mg per day increasing up to maximum dose of 960mg per day) found significant improvement in pain.

Ketamine:

This dissociative anaesthetic is an NMDA (N-methyl D-aspartate) receptor antagonist. NMDA is implicated in the centralisation of pain and sensitisation of the central nervous system via the "wind-up" mechanism. It has been used as an anaesthetic for many years and only recently has its application as an analgesic been explored. In 1994, studies ([631]) found ketamine to be effective in treating post-herpetic neuralgia (PHN).

Mercadante et al ([632]) recommended a starting dose of 150 mg/day, which they stated would allow the dose of opiate medication to be significantly decreased. In one patient whose case they presented, the treatment was effective over a studied period of 13 months.

Various other authors have described ketamine's properties in combating centralised pain ([633] [634]) but there have been no large studies of its use in chronic pain.

Ketamine has been used long-term in a few small studies. Klepstad et al ([635]) treated a patient with PHN using a combination of ketamine and dextromethorphan (another NMDA antagonist) administered via various routes, without serious side effects for 4 years.

Intravenous ketamine: "Ketamine is an adjuvant analgesic for the treatment of cancer-related pain when other agents either fail or are intolerable." ([636])

Ketamine ointment: a recent Japanese study ([637]) looking at the effects of 0.25-1.5% ketamine ointment in patients with CRPS types I and II found that it "appears to be beneficial for the patients with acute early dystrophic stage of CRPS I because of either its local anesthetic effect or NMDA receptor antagonist action. Patients with chronic atrophic stage of CRPS I and CRPS II patients do not appear to respond to this treatment."

LOCAL ANAESTHETIC AGENTS

Lidocaine: this local anaesthetic agent has been found to be helpful when used topically but also as an intravenous infusion. A recent paper in the journal Pain ([638]) noted that "continual systemic infusion of lidocaine prevents or reverses the development of neuropathic pain following chronic constriction injury". A recent UK study ([639]) looking at the effects of a 5% lidocaine patch in moderate to severe neuropathic pain (as measured on the Neuropathic Pain Scale) found that the patch "reduces the intensity of all common neuropathic pain qualities".

Mexiletine:

Mexiletine is a local anaesthetic that has been used to treat heart rhythm disorders.

Unlike externally used local anesthetics, mexiletine only appears to affect the painful nerves and thus neither numbs nor desensitizes the patient. It is sometimes used to treat diabetic neuropathy.

In 1997, The Mexiletine Study Group conducted a study on the safety and efficacy of mexiletine .([640]) They found "A significant reduction in sleep disturbances and pain during night time was observed in the group of patients taking the highest dosage (675 mg/day) of mexiletine compared with the other groups." They concluded that "Mexiletine in a dosage of 675 mg daily can reduce pain caused by diabetic neuropathy, and the effect of this drug appears

to have a rapid onset." No serious adverse effects were seen. Mexiletine has now become widely used to combat cancer-related neuropathic pain. Mexiletine is the preferred drug as it has a favourable side-effect profile ([641]) It may be considered as a second-line agent in treating refractory neuropathic pain.(of any origin). It could be used if, say, an antidepressant or anticonvulsant drug fails to be effective. The starting dose should be low, at 100- 150mg/day and be increased gradually until effective or side-effects become troublesome (max. dose 900mg/day i.e. 300 mg tds.). ECG readings should be monitored during dose escalation and plasma levels should be measured at higher doses.

ADRs: generally well tolerated. Adverse effects may include gastrointestinal distress, dizziness or light-headedness, tremor, and coordination difficulties. Mexiletine may worsen pre-existing cardiac arrhythmias and is contraindicated in patients with pre-existing second- or third-degree atrioventricular blockade.

Tocainide is one of the other alternatives. It has been found to be useful in treating trigeminal neuralgia.([642])

Muscle relaxants may be needed, including benzodiazepines such as diazepam (Valium). For increased muscle tone (spasticity) **Baclofen** (Lioresal®) is a useful drug. Baclofen is a GABA-agonist, although its exact mechanism of action remains uncertain. It is known to reduce release of excitatory neurotransmitters.

Baclofen does not affect neuromuscular transmission. It is primarily a drug used to treat spasticity (i.e. increased muscle tone) and spasm of skeletal muscles seen in neurological conditions but has also proved to be effective in the treatment of trigeminal neuralgia and has since been found useful in all types of neuropathic pain, especially if paroxysmal. It is now widely used. A starting dose of 5 mg once a day, increasing to two to three times per day is gradually escalated by increments of 5mg per day as tolerated to 30-90 mg per day, and possibly higher if side effects permit. It may be helpful to time the increase of dose for the bedtime dose, to minimise the impact of side effects. The most common adverse effects are sedation and confusion, which are due to the central nervous system depressant action of baclofen. However, a further problem may be hypotonia (decreased muscle tone) and weakness, which can compound pre-existing weakness due to the neurological condition being treated. Conversely, Baclofen-induced dyskinesia (abnormal movements) may occur.

Note however that sudden discontinuation of this drug must be avoided because of the high risk of seizures. In particular, there have been warnings about abrupt discontinuation of intrathecal baclofen because of the risk of high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity, (in rare cases this has advanced to rhabdomyolysis, multiple organ-system failure and death.) In order to avoid this, baclofen should always be discontinued by gradual dose reduction over at least 1-2 weeks. If symptoms occur, it may be necessary to prolong the gradual reduction.

Tizanidine (Zanaflex®) is a relatively new, centrally acting, alpha$_2$-adrenergic agonist that has been approved for the treatment of spasticity, such as that occurring in patients with multiple sclerosis or spinal cord injury. This agent is believed to act like norepinephrine by inhibiting polysynaptic pathways involved

in the activation of motor neurons. Chemically related to clonidine so it may cause hypotension (low blood pressure). Side effects are minimal: slight sleepiness and dry mouth.

Other anti-spasmodic drugs include:

Dantrolene (Dantrium®): acts directly on skeletal muscle and therefore has fewer central adverse effects.

Carisoprodol (Soma®)

Cyclobenzaprine (Flexeril®)

Metaxalone (Skelaxin®)

Methocarbamol (Robaxin/Robaxisal®)

Orphenadrine (Norflex/Norgesic/ Norgesic Forte®) : a derivative of the antihistamine diphenydramine (Benadryl).

Quinine sulfate (Quinam®): particularly for nocturnal cramps

Diazepam: to relieve muscle spasms, dose is 2-15mg daily in divided doses up to 60mg daily if necessary. In the context of chronic pain, drugs from this class (benzodiazepines) are quite commonly prescribed for 4 main reasons:

1. To treat anxiety/agitation secondary to chronic pain (Anxiolytic)
2. To treat sleep disturbance due to pain (Hypnotic)
3. To treat muscle spasm or spasticity (Muscle relaxant)
4. As potentiators of opiate drugs.(Adjuvant analgesic)

Clonazepam (Klonopin/Rivotril®):

Muscle relaxant: may be used to treat myoclonus (muscle jerks) especially nocturnal myoclonus

Clonazepam has also been found to reduce involuntary muscle hyperactivity which may arise due to chronic high dose opiate therapy.([643])

Anticonvulsant: 1mg initially at night for 4 weeks, increased over 2-4 weeks to a maintenance dose of 4-8mg daily in divided doses. May decrease in effectiveness after months of continuous therapy.

Pain relief: it has been used for trigeminal neuralgia with some success

The most frequently occurring adverse effects of clonazepam are due to central nervous system depression. Drowsiness occurs in approximately 50% of patients and ataxia (drunken gait) in approximately 30%. Behaviour problems have been noted in approximately 25% of patients and increased salivation in 7%. Often, the sedative side-effects subside after a time.

Alprazolam (Xanax): dosage: 0.25mg to 1.5mg daily.

A study of cancer patients ([644]) found that it was helpful in relieving neuropathic pain

However, it is used primarily for short-term relief of mild to moderate anxiety and nervous tension, symptoms of PMS, tinnitus and essential tremor.

Ashton ([645]) has expressed the opinion: "Alprazolam has been widely used, particularly in the US, but is not recommended in the UK, especially for long term use."

Peter Breggin MD wrote the following in his book "Brain-Disabling Treatments in Psychiatry: Drugs, Electroshock and the Role of the FDA" in 1997 ([646])

"Studies of Xanax show that most patients develop withdrawal symptoms during routine treatment lasting only 8 weeks."

Within 2-4 weeks tolerance can develop to the sedative effect of minor tranquillisers taken at night for sleep.

Short-acting BZDs can produce especially severe withdrawal symptoms (this includes Xanax, Halcion, Ativan, Restoril and Serax).

Note:

Benzodiazepine use carries a high risk of addiction and tolerance that can develop rapidly within a couple of weeks of starting treatment; however, withdrawal symptoms tend to occur only in about 50% of people. There is a wide range of symptoms. Withdrawal symptoms after stopping a long-acting BZD may not develop for up to 3 weeks after last dose, whereas with short-acting drugs they occur within a few hours (hence the possibility of inter-dose withdrawal symptoms.)

CLONIDINE

Clonidine is an alpha-2 adrenergic agonist that has been used for many years as an antihypertensive drug (treating high blood pressure) It has also been found to have analgesic effects in migraine, post-operative pain, post-herpetic neuralgia and diabetic neuropathy. Spaulding et al ([647]) noted that it can potentiate morphine analgesia. The transdermal preparation has been reported anecdotally ([648]) to decrease the pain of CRPS (Reflex sympathetic dystrophy) if applied to the affected extremity.

Often clonidine is administered via the epidural route in conjunction with other analgesia. In the cancer population, a trial of oral or transdermal clonidine may be considered in the management of persistent neuropathic pain refractory to opioids and other adjuvants.

Clonidine is available in 0.1 mg tablets, but the Catapres® patch (0.1 mg and 0.2mg) is designed to deliver the specified dose daily and must be changed every seven days. A trial should commence with very low doses e.g. start at 0.1mg at bedtime and increase gradually. Side effects include sedation (the major side effect) bradycardia (slow pulse), hypotension (low blood pressure), dry mouth, constipation, dizziness and depression. Postural hypotension (drop in blood pressure on standing up) is a common adverse effect, which may limit the dose that can be tolerated.

NIFEDIPINE

Nifedipine is a calcium channel blocker usually used to relieve angina pain and to reduce mild to moderate hypertension (raised blood pressure). However, it has also been found to be helpful in neuropathic pain such as that in CRPS (Complex Regional Pain Syndrome, also known as RSD Reflex Sympathetic Dystrophy). Ohta et al([649]) reported that a case of RSD responded favourably to sublingual nifedipine. A testing dose of 10mg gave relief of pain in 10 minutes, lasting 6 hours. Regular dose of 30-60mg daily was successful in reducing symptoms, which had markedly improved within 4 weeks. At 3 months, there was

complete resolution of pain and although it has recurred from time to time, nifedipine has successfully reduced it again each time.

Non-steroidal anti-inflammatory drugs (NSAIDs)

This group of drugs exerts its effect via enzymes involved in inflammatory pathways, Cyclo-oxygenase types 1 and 2. Type 1 is called 'constitutive' because it is always there. Its functions including protection of the stomach lining, maintenance of renal blood flow, vascular and platelet function.

COX-2 is an 'inducible' enzyme that is expressed in the presence of inflammation; it has also now been shown to be present all the time in the kidney.

COX-1 inhibitors: e.g. ibuprofen, diclofenac may cause significant gastrointestinal side effects as well as occasionally kidney problems after prolonged use ((Note that a significant proportion of patients who sustain a serious gastric adverse event (e.g. a bleeding ulcer) have no preceding warning symptoms such as heartburn or epigastric pain.))

COX-2 inhibitors (e.g. Celebrex, Vioxx), the new type of NSAID, are as beneficial as traditional NSAIDs but are thought to carry a lower risk of gastrointestinal adverse effects.

Celecoxib (Celebrex) may be used for acute pain at a dose of 400mg initially and 200mg prn (as required) on the first day and then 200mg twice a day as required. In Rheumatoid arthritis, a dose of 100-200mg twice a day is used.

Rofecoxib (Vioxx) is used for acute pain at 50mg four times a day and for Rheumatoid arthritis at 25mg four times a day.

However, COX-2 inhibitors carry the same significant risks of cardiorenal adverse effects such as hypertension, fluid and electrolyte abnormalities, congestive heart failure, renal failure etc. as other NSAIDs.

This type of drug is not generally effective for the relief of neuropathic pain. NSAIDs can however be helpful in relieving musculoskeletal pain including joint pain, which can arise as secondary features. As arachnoiditis has an inflammatory component, some patients find that NSAIDs help to reduce the impact of a 'flare-up'.

Protection against the gastric side effects may be achieved using proton pump inhibitors such as Losec.

Topical capsaicin:

Capsaicin (Zostrix®) is the active component of cayenne pepper and is responsible for its pungent and irritating effects. A specific receptor activated by capsaicin (termed vanilloid receptor subtype 1 orVR1) is implicated in both the treatment of chronic pain and urinary incontinence.

Repeated applications deactivate the capsaicin receptor: overstimulating the receptor may destroy the sensory nerve endings. Repeated administration of Capsaicin depletes peripheral neuropeptides, notably Substance P that is known to be essential in pain transmission and is involved in inflammatory conditions

such as arthritis. It is therefore most useful for pain of peripheral origin, such as postherpetic neuralgia or diabetic neuropathy.

Commercial ointments containing 0.025% or 0.075% capsaicin are available. These preparations (particularly the higher strength preparations) may offer significant benefit in a number of conditions including the pain associated with peripheral neuropathy and arthritis, when it appears to relieve some of the burning. The cream should be applied twice daily to the affected areas. Many patients find the initial (expected) increase in pain (which occurs prior to the anaesthetic effect) is intolerable, and this may limit its use.

In June 2000, McCleane reported ([650]) results of a study of **t**opical application of doxepin hydrochloride, capsaicin and a combination of both and found that they produce analgesia in chronic neuropathic pain. He used 3.3% doxepin hydrochloride, 0.025% capsaicin and a combination of 3.3% doxepin and 0.025% capsaicin. He found that "The analgesia with doxepin/capsaicin was of more rapid onset. Capsaicin significantly reduced sensitivity and shooting pain. Burning pain was increased by doxepin and by capsaicin and to a lesser extent by doxepin/capsaicin."

Disadvantages include

- Initial discomfort
- Does not begin working right away, possible long delay (2-6 weeks)

Proper use of capsaicin:

- It is advisable to put on a glove first to ensure against inadvertently rubbing the eyes or touching sensitive skin with fingers contaminated with the medicine.
- Do not apply to broken skin.
- Rub it into the skin of the affected area completely.
- Capsaicin may sting at first. This burning usually lasts only lasts a few days, but for some users it may be quite some time before it dissipates.
- The medicine must be applied every day. Skipping doses will not help and will in fact prolong the amount of time it takes before the burning reduces. Apply the medicine three to four times a day. Must continue be applied consistently several times a day

Isosorbide dinitrate: this is the spray used by people with heart conditions. It has recently been found to be effective in diabetic neuropathy. A study at Addenbrooke's Hospital in Cambridge ([651]) found that 50% of patients gained relief. The authors concluded: **"**ISDN spray offers an alternative and effective pharmacological option in relieving overall pain and burning sensation in the management of painful diabetic neuropathy."

A recent Greek study ([652]) looking at treatment of post-operative pain after surgery for breast cancer, found that a combination of gabapentin (1200mg/day) and mexiletine (600mg/day) were ineffective in preventing

chronic pain except burning pain which was reduced. However, an animal study ([653]) showed that mexiletine was effective in a model of neuropathic pain (spared nerve injury) in reducing both cold allodynia and mechanical hyperalgesia, with the most distinct and prolonged effect on mechanical allodynia.

Miscellaneous:

Some patients have found that the troublesome nocturnal muscle cramps may be relieved by **quinine,** found in drinks such as Indian Tonic Water.

TREATMENT OF VISCERAL PAIN

Painful bladder or rectal spasms may occur in some conditions.

For painful bladder spasms, non-steroidal anti-inflammatory drugs may be helpful due to the possible role that prostaglandins play in bladder muscle contraction.

Painful rectal spasms may respond to **diltiazem**, a calcium channel blocker that reduces smooth-muscle contraction, which has been effective in the management of proctalgia fugax (shooting pains in the rectum). ([654]) Chlorpromazine (a neuroleptic) ([655]), and benzodiazepines ([656]) have also been used and their efficacy noted anecdotally.

TREATING EXACERBATIONS OF CHRONIC PAIN

Exacerbations of chronic pain may cause patients to present to the emergency department with acute episodes, commonly of back or abdominal pain. Of course, there may also be acute conditions, which occur that are unrelated to the chronic condition, or post-operative analgesia is required.

In this situation, the usual medication is insufficient to provide analgesia but will interact with any treatment given for the acute condition. If the patient is on opiate medication, they will have developed tolerance to the effect not only of the medications they are taking, but also a degree of cross-tolerance to the effect of other opioid drugs. This cannot necessarily be accurately predicted, as it will vary between individuals. It is not within the scope of this article to address the complexities of prescribing under these conditions.

However, it is worth noting Mehl-Madrona's study published in 1999([657]). This looked at use of a combination of keterolac and chlorpromazine to replace the more usual meperidine/promethazine combination in the emergency room for exacerbations of chronic pain. Keterolac is a potent Non-steroidal anti-inflammatory drug (NSAID) that is indicated for moderate to severe pain (NOT mild pain), chlorpromazine is a neuroleptic. Meperidine (pethidine) is a short-acting opiate given intramuscularly and promazine is given to prevent nausea and vomiting which may be induced by meperidine.

.Patients were given either intramuscular doses of 60mg keterolac +50-75 mg chlorpromazine(KET-CHLOR) (depending on weight) or 50mg meperidine plus 25-50mg promethazine(MEP-PROM). (Heavier patients were given 1.5 doses). It was found that the pain relief of the 2 different protocols was comparable, but the

KET-CHLOR patients had fewer side effects and this combination worked better for nausea (chlorpromazine is a more potent antiemetic than promazine).

MANAGEMENT OF BREAKTHROUGH PAIN

Multiple modalities can be used.

1. Increase in dosage of round-the-clock analgesia: this may mask moderate exacerbations, but is less likely to help with severe exacerbations. However, there is greater likelihood of side effects from the increased medication levels, particularly when the exacerbation has abated.
2. Supplemental ('rescue') analgesics: preparations such as Actiq® which have a rapid onset of action and short duration can be helpful, especially with predictable pain: the lozenge can be taken just ahead of planned activity.
3. Non-pharmacological measures: changes in body position and movement; massage
4. Rigorous management of trigger factors: such as constipation, cough etc.
5. Anticonvulsants: may be the most effective treatment for lancinating pains.
6. Local techniques: allodynia triggered by light touch (e.g. clothes) may be relieved by application of lidocaine gel.
7. Cognitive techniques: as described below.

THE USE OF DRUGS BEYOND LICENCE

The majority of medicines prescribed or purchased over the counter (OTC) have a licence for use, which is obtained by the manufacturer prior to being permitted to produce and sell the medicine in the UK. This is under the remit of the Medicines Control Agency (MCA), which issues a product licence or marketing authorisation. The licence describes the way in which the drug is given (route of administration e.g. oral or intravenous), the dose range and which patients it should be used to treat (indications). The manufacturer has to prove that the drug is effective for the condition for which it is given, does not have too many side effects or risks and that it has been manufactured to a high standard. The licence is designed to restrict the way in which the manufacturer promotes and sells the drug, but does not restrict the way in which doctors prescribe the medicine. It is entirely legal for doctors to prescribe drugs outside the licence. In palliative care, for example, up to two thirds of patients receive drugs under these circumstances, usually when there is no suitable licensed alternative. In the field of pain management, the use of drugs beyond their licence is sufficiently commonplace that it is unlikely doctors will make specific reference to this to patients when they are prescribing these drugs.

Obtaining a licence is a highly expensive undertaking for the manufacturer. If post-marketing research shows that there is an application for the drug to be used in a different way from the one specified in the licence, it may not be economical for the manufacturer to apply for an extended licence. There is no legal

requirement for the manufacturer to apply to the Medicines Control Agency to add the more recent information to the product licence.

However, there is a legal requirement for the manufacturer to include a Patient Information Leaflet (PIL) with all medicines. This can only contain information from the licence, so off licence use will not be covered. This means, for example, that the PIL for antidepressants will not cover their use for pain relief.

As well as off licence use with regard to indications (what it is being used for), drugs may be used outside their licence at different doses from the one licensed, or via a different route of administration (e.g. injection instead of tablets). The latter includes the use of epidural steroid injections, which are not licensed for use around the spine, although they are licensed for intramuscular injections and injections into joints.

Common drugs used beyond licence include antidepressants and anticonvulsants for pain relief.

A leaflet about this is available from the Pain Society at www.painsociety.org or www.palliative-medicine.org.

COMMON SIDE EFFECTS

Polypharmacy (the use of a 'cocktail' of drugs) carries a substantial side effect profile, which can adversely impact on quality of life.

The commonest side effects are:

- **Sedation**: is commonly a problem when commencing treatment, but may subside after 2-3 weeks. This can be a beneficial side effect to aid sleep at night.
- **Constipation**: a highly common problem that should never be underestimated. It may exacerbate low back pain and urinary incontinence. Treatment can be difficult. In the US, opiate-related constipation is treated with methylnaltrexone.
- **Dry mouth**: caused by various types of medication especially antidepressants.
- **Cognitive impairment** (fuzzy thinking): a distressing problem that can be hard to pinpoint but can nevertheless cause significant difficulties in daily life.
- **Sexual dysfunction**: quite a common side effect of most antidepressant drugs. As this may also be a problem due to the condition itself, onset of this symptom can be misdiagnosed: if medication-related, it is curable. Opiates may cause loss of libido.
- **Weight change**: a gain in weight is commonly experienced, particularly with anticonvulsants and also antidepressants. This can compound difficulties with mobility. Fluid retention due to opiates is one cause of weight gain. Some people can also experience weight loss.
- **Rash**: anticonvulsants in particular are associated with skin problems.
- **Allergy**: a significant number of arachnoiditis patients develop allergies to various types of medication, especially antibiotics. Some people develop multiple allergies.

- **Gastric upset**: NSAIDs are known to cause gastrointestinal problems including ulcers.
- **Addiction**: this is feared by patients and their families and a focus of concern by medical professionals. There is however ample evidence that when used at appropriate levels strictly for pain relief (not to aid sleep, or reduce symptoms of anxiety) then the risk is minimal. Some degree of tolerance may develop as receptor sites adapt to the new levels of opiates, but many patients do not find they need escalating doses of drug to maintain pain relief.

Invasive treatments

INA (Intraspinal narcotic analgesia)

The "pump": this was originally developed for use in terminally ill cancer patients when it was not being considered for long-term use. From the studies now performed of long term pump use emerge varying opinions as to its safety and efficacy. One recent paper states: "About one third of the patients get good long-term pain relief without complications or side effects, many require the addition of local anesthetics, and some never get effective relief. There are major questions to be answered before this form of therapy becomes widely disseminated."([658])

A recent study in the UK ([659]) showed that INA was effective as pain relief, for patients with failed back syndrome and chronic mechanical low back pain. Diamorphine was used in all 37 patients, bupivacaine in 32, clonidine in 27 and baclofen in 3. The mean dose of diamorphine increased for the first 2 years but did not change 2-6 years post implant, averaging 4.5 mg/day. Revision surgery was necessary in 24% of cases. The authors, Raphael et al. pointed out that whilst some authors had found tolerance requiring increasing doses, others had not. They found that the pain level reduced by 3 or more on an 11-point scale (0-10) which they regarded as clinically significant, with average implant duration of 4.38 years.

They remarked: "Spinal opioids for low back pain is a therapy of last resort and is controversial."

Spinal opiates affect spinal nociceptive processing by reducing the release of excitatory neurotransmitters and decreasing the excitability of dorsal horn neurons. Extensive literature indicates that opiates delivered spinally induce strong analgesia. The well researched pharmacology of this action has shown that μ, d and ?, opiate agonists are effective. Distribution of the opiate must extend beyond the spinal segment because sensory input into a given nerve root (from a specific dermatome) distributes several segments once the afferent has entered the dorsal root entry zone. (Compare delivery of a local anaesthetic, which is designed to affect a single root only). Small volumes and high concentrations may only be effective when there is adequate redistribution. This may be impaired in the case of arachnoiditis where CSF flow is compromised.

Opiates are often supplemented with either local anaesthetics such as bupivicaine, or antispasmodics such as baclofen.

Principal problems with intraspinal drug therapy include system failure, infection and neurotoxicity. System malfunction varies according to manufacturer, but tends to run at about 20 %([660]).

There are a number of papers documenting cases in which intrathecal granulomatous tissue has formed at the pump site. ([661]; [662]) Bearing in mind that this is a form of scar tissue, this has special relevance to

arachnoiditis patients who already have scarring problems. The suspected causes include: infectious process, hypersensitivity to implant materials, mechanical or chemical effect of the infusate, or local tissue (toxic/inflammatory) response to the drug.

A further paper ([663]) describes evidence of focal subdural fibrosis and discrete injuries to nerve roots in patients with intrathecal infusions of morphine and bupivicaine.

A report in a San Francisco newspaper in June 2002 described cases of granuloma that are becoming ever more frequent and may be related to compounded opiate preparations being used to refill the pump. FDA-approved morphine for pump use (Infumorph) is not being used, instead mixtures of opiates with other agents are being prepared to cut costs and boost the income generated. The newspaper article suggested that whilst a paper by Burchiel in the journal Neurosurgery stated 41 cases, in fact the number of cases to date was at least 74. Interestingly, the Medtronic representative (who estimates that 30,000 patients in the United States are wearing portable infusion pumps) told the journalist that he did not attribute these granuloma cases to compounded drugs. He stated that they have occurred in patients using FDA-approved morphine, so that he thought that the inflammation might be a chemical irritation "related to the properties of morphine itself." Scott Ward, president of Medtronic's neurological and diabetes division, stated, "The fact of the matter is we do not know with medical certainty what causes these granulomas."

Coffey and Burchiel ([664]) reported on 41 cases of inflammatory mass lesions at the tip of intraspinal drug administration catheters. They commented: "Because of voluntary reporting and other methodological limitations, the actual number of cases must be higher than reported." The patients all had chronic pain and on average had had the pump for around 2 years. Most masses were in the thoracic region. 30 patients underwent surgical decompression. They remarked: "The most plausible hypothesis with regard to the cause of intrathecal catheter tip mass lesions implicates the administration of relatively high-concentration or high-dose opiate drugs or the use of drugs and admixtures that are not labeled for intrathecal use."

Reported symptoms associated with the development of an inflammatory mass:

- Drug withdrawal symptoms
- Progressive change in character, quality or intensity of pain
- Considerable increase in the level and degree of pain despite dose escalation
- Sensory changes (i.e. numbness, tingling, burning, etc.)
- Hyperesthesia, hyperalgesia
- Sleep disturbances
- Bowel and/ or bladder dysfunction
- Myelopathy
- Conus syndrome
- Gait disturbances/ difficulty ambulating
- Paraparesis/ paralysis

Patients receiving long-term intraspinal therapy should be carefully monitored if any of these symptoms are observed.

These findings are of some concern considering a recent paper ([665]) on the use of INA in the UK for FBSS and chronic mechanical low back pain.
Other adverse effects of INA such as constipation, nausea, vomiting and itching tend to be short-term, whereas loss of libido and potency may persist for several months. The most persistent side-effects are sweating and oedema (swelling), the latter of which may necessitate INA being discontinued. The most serious adverse effect is respiratory depression.
High concentrations of morphine may lead to allodynic effects that are not opiate receptor mediated but may be due to the metabolite. Chronic delivery of intrathecal morphine in high concentrations has been demonstrated as leading to the formation of aseptic inflammatory masses (granulomas).

Penn and Paice suggested the following prevalence of side effects: ([666])
Nausea and vomiting 25.2%
Pruritis 13.3%
Oedema 11.7%
Diaphoresis (sweating) 7.2%
Weakness 7.2%
Weight Gain 5.4%
Diminished Libido 4.9%

Aldrete, writing about leg oedema from intrathecal opiate infusions ([667]), noted that 5 patients who had had the pump for more than 24 months developed leg and feet oedema; they all had a previous history of foot oedema and venous stasis prior to pump insertion. The complication caused lymphoedema, ulcerations and hyperpigmentation of the skin. The severity of the oedema reduced as the morphine dose decreased, and in 2 cases where the infusion was discontinued, the oedema resolved completely.
Aldrete suggested that pedal oedema and vascular stasis are relative contraindications for pump therapy.

A consensus conference on the continuous infusion of spinal drugs for chronic pain management, saw several points raised: morphine is the principle agent employed; doses up to 20 mg/day are "acceptable" and concentrations should be adjusted to allow as long an interval between refills as possible ([668]).

The pump and MRI scans: whilst an MRI will temporarily stop the pump motor and suspend drug infusion, the pump should resume normal operation after the MRI had finished. During the MRI scan, the patient may experience heating or peripheral nerve stimulation at or near the pump implant site.
(Tesla) MR scanners -- it is not recommended that patients have MRI scans using these scanners.

Note: Intrathecal Baclofen

Sampson et al. ([669]) recently conducted a review on the use of intrathecal baclofen in treating severe spasticity. They concluded that this treatment "produces functional benefits and is likely to be an appropriate use of resources in carefully selected patients." They specified that patients must have severe, disabling spasticity that remains refractory to oral medication. Fortunately, most arachnoiditis patients do not seem to have this degree of spasticity.

Prescribing information about baclofen (Lioresal) intrathecal injection now includes a warning about possible problems following abrupt discontinuation of treatment, including high fever, altered mental state, exaggerated rebound spasticity, muscle rigidity and in rare cases rhabdomyolysis, multiple organ failure and death. In order to avoid this, careful attention to possible signs of baclofen withdrawal as a result of pump system failure for example, must be maintained. These signs include spasticity, pruritus (itching), hypotension (low blood pressure) and paraesthesiae.
Some of the clinical characteristics of withdrawal may resemble autonomic dysreflexia, infection, neuroleptic malignant syndrome, malignant hyperthermia or other syndromes associated with a hypermetabolic state. Should it be impossible to reinstate the infusion, GABA agonists should be administered orally (baclofen or benzodiazepines).

Spinal Cord Stimulation (SCS)

Spinal Cord Stimulation or SCS is a technique involving electrical stimulation of a precise part of the spinal cord. A very low energy current is used. This essentially shuts down the pain signals from the part of the body served by that area in the spinal cord. Whilst providing pain relief, other sensory input is not affected and there is normal motor (muscular) function. Basically, the theory behind SCS is that sending non-painful signals will block out the painful ones: in much the same way as we instinctively rub our hand if we have banged it.
Instead of feeling pain, the patient will experience tingling.
Two carefully positioned leads (insulated) with electrodes on the end are placed adjacent to the spinal cord: one end rests in the epidural space whilst the other is attached to a battery operated (9v) signal generator.
The **Implantable pulse generator (IPG)** is titanium-encased and it supplies the energy for stimulation. It contains a special battery and electronic circuitry. It is approximately 60 mm (2.5 inches) at the longest point and 52 mm (2.25 inches) at its widest point. It is about 10 mm (0.4 inches) thick.
The receiver is surgically implanted, usually in the patient's abdominal area. It contains electronic circuits but no battery. The receiver receives electrical pulses from the transmitter and sends them via the leads to the electrodes next to the spinal cord or, in some cases to a peripheral nerve.
The external transmitter may be worn on a belt. It sends radiofrequency signals to the electrodes; amplitude, pulse width, and rate of the electric pulse can be varied non-invasively. There is also an antenna that is positioned over the implanted receiver.

Patients who are considered suitable for SCS first undergo a trial in which a lead is implanted in the epidural space and stimulation applied. If the patient finds that this is helpful then the full system will be implanted.

RESULTS WITH SCS:

Kumar et al ([670]) looked at 121 patients using SCS for a variety of painful condition. They concluded that epidural SCS is safe and effective on the basis that 40% of the patients were able to control their pain with neurostimulation alone whilst a further 12% required the use of analgesics to achieve more than 50% pain relief. "Pain secondary to arachnoiditis or perineural fibrosis following multiple intervertebral disc operations, when predominantly confined to one lower extremity seemed to respond favorably to this treatment."

They noted that pain due to cauda equina injury, paraplegic pain, phantom-limb pain, pure midline back pain without radiculopathy, or pain due to primary bone or joint disease was less responsive to SCS.

However, the Pain Management Center of the University of Utah Hospitals and Clinics website ([671]) reports much less encouraging figures:

"Outcome:

55% report initial relief

Relief after 6 months 33%

Relief after 2 years 12%

Relief after 10 years 5%"

The progressively lower success rate over time is attributed to fibrosis around the electrode tip, pain spreading to areas not covered by the electrode and breakdown of the system.

Long ([672]) cited an immediate success rate of <70%, intermediate <50% and long term <30%. He favoured this form of therapy as standard when pain is a major problem. Midha and Schmitt ([673]) have looked at the use of SCS in spinal cord injury patients to treat pain and spasticity (increased muscle tone, muscle spasms). They have stated, "The epidural spinal cord stimulator lacks long-term efficacy for the relief of spasticity and pain and is not cost effective."

Kay et al. from Dundee ([674]) looked at SCS as an established treatment for chronic pain, angina and peripheral vascular disease over a 13 year period. The retrospective study of 70 patients who had severe pain refractory to other treatment, showed that there were 72 surgical revisions (electrode repositioning/replacement, generator replacement, cable failure) of which 12 were implant removals. Half of the devices were revised within 3 years. 6 implants became infected.

60% of the patients reported substantial pain relief. This is the level of success reported by Dr. Charles Burton in some 1200 or so procedures performed over the past 25 years for relief of intractable pain secondary to adhesive arachnoiditis ([675]) . However, it should be noted that Dr. Burton is a neurosurgeon and this level of result may not be achieved with less experienced practitioners.

Midha et al. ([676]) investigated SCS as treatment of spasticity and spasms following spinal cord injury (these are common problems in arachnoiditis). 7 out of 17 patients required a second implantation and in only 1

was there any symptomatic relief. The authors therefore concluded: "The epidural spinal cord stimulator lacks long-term efficacy for the relief of spasticity and pain and is not cost effective".

Devulder et al. ([677]) in Belgium, looked at SCS use in Failed back surgery syndrome. 26 of 69 patients stopped using this treatment, of which in 10 there was no clear reason. 43 obtained "good pain relief". Some still required opioid analgesics in addition to the SCS.

Hieu et al. ([678]) found that in FBSS patients, "Long-term efficacy was good in 63.6% of cases, fair in 22%, and poor in 6.5%; treatment failure occurred in 7.9% of cases. Adverse events included one case of meningitis, two cases of local infection, and one case each of cerebrospinal fluid fistula and necrosis of the skin overlying the stimulator. The main causes of treatment failure were complications, inappropriate patient selection, and the escape phenomenon."

Van de Kelft and De La Porte ([679]) treated patients with pain in one or both legs. 54% continued to experience at least 50% pain relief during a mean follow-up period of 47 months. 91% were able to reduce their medication intake and 60% reported an improved lifestyle.

LeDoux and Langford ([680]) reported that 76% of patients with FBSS at 1 year and 74% at 2 years were still experiencing 50% or better pain relief. Electrode migration was the most common complication.

De La Porte and Van de Kelft's earlier study showed ([681]) 55% continued to experience at least 50% of pain relief for a mean follow-up of 4 years. 90% were able to reduce their medication, 61% reported improved lifestyle.

North et al. ([682]) found a success rate (at least 50% sustained pain relief and patient satisfaction) in 53% of patients at 2.2 years and in 47% of patients at 5.0 years postoperatively.

Manufacturers Medtronic state "Typically, people who find the therapy helpful experience 50%-70% pain relief." ([683])

Meilman et al ([684]) also state that SCS is of greater efficacy for unilateral lower limb pain than for more widespread nerve root involvement. It is best for controlling the dull, constant pain and poor for the sharp, lancinating pain. SCS may also be useful for neurogenic bladder problems. ([685])

In Chapter XXIII, Aldrete and Ghaly describe electrical stimulation techniques, such as spinal cord stimulation (SCS). The authors conclude "Still rather unpredictable as far as long-term results is concerned; SCS has potential to provide pain reduction, but not real pain relief." Patients with one limb affected have the best chance of success. Brain stimulation "may be more promising when technological advances will make it non-invasive."

ADVERSE EFFECTS OF SCS include:

Infection, bleeding, haemorrhage, haematoma, headache, hardware difficulties, spinal cord injury, allergic reactions, paralysis, pain at implant site. Kumar et al. noted in particular: Complications included wound infection, electrode displacement or fracturing, and fibrosis at the stimulating tip of the electrode.

General complications with the system include: no stimulation or intermittent stimulation, stimulation in the wrong location, loss of pain relieving effect and allergic response to system.

IMPORTANT NOTE:

Anti-theft and metal detector systems may affect spinal cord stimulators, due to the effect of their electromagnetic fields. These security systems may cause over stimulation, and patients will report pain, jolts and shocks.

SURGICAL INTERVENTION

Surgical treatment is generally regarded to have a low success rate.

Many patients fall into the category Failed Back Surgery Syndrome (FBSS). Burton et al ([686]) pointed out,

"Nerve compression can be relieved surgically but pain due to nerve injury or scar tissue can only be reduced in extent by therapy ...physical and emotional reactivation in chronic pain programmes..."

"The answer to the problem is not better FBSS salvage, but avoiding the causes of failure of lumbar spine surgery."

Resection of scar tissue is often followed by recurrence. Some specialists are now using laser techniques, but data on the outcomes is limited.

Aldrete made the following comment in his chapter on surgical treatment:

"such interventions (are) hazardous, especially when it is realized that the arachnoid membrane may react in some patients with an exaggerated inflammatory response, ensuing in further adhesions, more extensive scarring, cicatrix, and even ossification processes."

Adhesive arachnoiditis and epidural fibrosis following lumbar laminectomy may obscure the planes between the nerve roots and the thecal sac and the epidural space and the ligamentum flavum may be indistinguishable within the scar. Dissecting through this scar risks inadvertent injury to neural structures with possibly devastating functional consequences (such as a foot drop) for the patient.

Aldrete states that patients undergoing Lumbosacral spinal surgery should consider the following conditions and complications (in ascending order of severity), which indicate a worse prognosis:

- Spondylosis
- Radiculopathy
- Epidural scarring
- Arachnoiditis

In his list of surgical principles for prevention of arachnoiditis, Aldrete lists avoiding unnecessary spine surgery.

As Aldrete points out, we nevertheless need to consider the surgical option in 3 types of patients:

- Patients with arachnoiditis who require surgical intervention for an acute problem such as a herniated disc.
- Patients requiring spinal fusion
- Patients who require surgical intervention to treat one of the lesions caused by arachnoiditis e.g. syrinx.

Johnston and Matheny in 1978 ([687]) looked at 28 arachnoiditis patients, performing an extensive laminectomy and irrigation with chymotrypsin, followed by microscopic dissection of arachnoid adhesions. Oral cortisone was given for 5 days post-operatively. The patients were followed up for 7 years. Comparing their results to a similar series by Jorgensen et al., the authors concluded that although the operation was feasible, only extremely select cases should be operate upon.

Shikata et al. reported a new technique in 1979 ([688]), in which they performed both microlysis of adhesions and spondylodesis for symptomatic spinal adhesive arachnoiditis. Good results were obtained by nonmicroscopic lysis and microlysis in only 54.8%, but when microlysis was followed by spondylodesis, the success rate increased to 80%.

Benini and Blanco ([689]) and Martynov et al ([690]) were of the opinion that only progressive, severe loss of function warranted surgical intervention. Roca et al ([691]) classified 40 arachnoiditis patients into four types and concluded that patients with diffuse sensory deficit, neurogenic claudication, bladder dysfunction and dysaesthesias were likely to have poor operative outcomes.

Laus et al. ([692]) noted that in all cases with previous arachnoiditis, further surgical intervention worsened the symptoms, as was also demonstrated by Marchetti et al. ([693])
Various authors have emphasised the need for surgical techniques that reduce tissue trauma (e.g. Carroll and Wiesel ([694]), Wilkinson ([695]) and Burton ([696])).

In their review of 146 malpractice cases, Goodkin and Laska ([697]) suggested that complications such as Cauda Equina Syndrome, incidental durotomy, nerve root injury and pseudomeningocele were to some extent unavoidable, although possibly related to 'substandard technique'.

Various recommendations as to ways in which to prevent or ameliorate arachnoiditis include: meticulous attention to good haemostasis to prevent blood accumulation, avoidance of local irritants such as Gelfoam® with repeated irrigation to clear them, avoidance of opening the dura, and gentle handling of the neural tissue which is of paramount importance.

Attempts at scar prevention with collagen inhibitors have included use of various methods such as those with barrier gels, which act as "interpositional" membranes. One of these, Adcon-L initially showed promise that now fails to deliver. Richter et al. ([698]) in 2001, looked at nearly 400 patients at 8 neurosurgical centres in Germany between 1994 and 1998 and "found no positive effect of treatment with ADCON-L gel in patients in whom one-level lumbar microdiscectomy was performed". This product, reputedly safe and effective in preventing epidural scarring by blocking the ingrowth of fibroblasts, has not been proven useful in repeated spinal surgery. Indeed, it may be that the presence of this foreign material is itself a focus for further inflammatory reaction in susceptible individuals and may thus result in exacerbating rather than

alleviating the scar tissue. (Note: Adcon-L is no longer available; micro-contaminants led to its withdrawal from the market).

Kemaloglu et al. ([699]) recently published the results of a rat study on the use of recombinant tissue plasminogen activator (rt-PA) in preventing postlaminectomy epidural fibrosis. They reported, "Findings suggest a beneficial effect of rt-PA in decreasing the epidural fibrosis following laminectomy when compared with control groups for all investigated parameters such as intermuscular scar (P=0.04), middle scar (P=0.001), deep scar (P=0.001) and dural adhesion (P=0.01) except new bone formation. The presence of arachnoiditis was less in treatment group (P=0.01)." Further investigation is required, but the authors optimistically suggest, "Thrombolytic therapy with rt-PA after spine surgery may come to play an important role in the prevention of epidural fibrosis and arachnoiditis."

Burton suggests that to date autogenous fat grafting is the "best means developed" for dealing with post-operative epidural scar, with revascularised fat tissue protecting the dura. ([700])
Use of steroids perioperatively has shown mixed results. Ota et al. ([701]) showed apparently improved outcomes, whereas Manniche et al. ([702]) failed to demonstrate any difference between this and placebo in patients undergoing first spinal surgery.

Decompressive surgery to remove adhesions remains controversial and the minimally invasive techniques have yet to be demonstrated as useful. Lazar and Bland ([703]) used microlysis of the adhesions in patients with arachnoiditis, followed by application of a silastic dural graft, but failed to show significant benefit. Nussbaum et al. had only minimally positive results using Polyglactin 910 as a dural substitute. Poloxamer 407, a non-ionic block copolymer which is cited as having "extremely low dermal and mucosal toxicity," has been found to reduce peritoneal and uterine horn adhesions, and in a rabbit study ([704]) produced a 50% reduction in leptomeningeal adhesions when applied intradurally and peridurally, without apparently affecting the neurological function or structure of the spinal cord of peripheral nerves.

The authors close by reminding the reader, "lesions of ARC go beyond the anatomical injuries, and also include functional alterations of the dorsal horn of the spinal cord."

Long([705]): in his first series operating on patients for pain, direct operation with microlysis of adhesions had a success rate of 55% at 5 years, although 13% developed significant worsening of bladder and bowel function. In the second series, operation was reserved for those with clearly progressive neurological deficit. 12 patients were operated on, of which 5 gained satisfactory pain control, although this was not lasting. In 9, neurological deficit was stabilised or improved (of which 5 experienced significant improvement in strength). Neither sensory nor bladder/bowel dysfunction were changed. Long therefore suggests that the majority of patients are not candidates for direct operation, reserving it for those with severe progressive problems with the aim of stabilising the loss of function.

Warnke et al. in Germany ([706]) recently published a series of articles on thecaloscopy, in which they advocate this procedure for conditions involving "arachnitis". They looked at 9 patients with suspected arachnoiditis that was not imaged on MR as well as 3 cases with established diagnosis (e.g. arachnoid cyst) and reported: "The pathomorphology of the arachnoid was detected and endoscopically treated in almost all cases. Arachnoid cysts were successfully fenestrated and an intraspinal meningocoele treated with endoscopic assistance." In cases of arachnoiditis with Hoffman grade 2 and 3 adhesions, these were successfully dissected and inflammatory tissue removed, but grade 4 adhesions were impossible to remove. In 45% of patients the pre-operative pain disappeared completely and did not recur for a period of 6 months. The other 55% experienced a significant reduction in pain (to 40% of pre-operative levels). Aside from headache, no serious adverse events occurred.

The authors conclude: "Thecaloscopy is a safe procedure if skilfully performed. It provides an opening for a wide range of new diagnostic and therapeutic options."

However, Burton stated: ([707]) "The patient with a minimally invasive procedure is at significantly higher risk of developing recurrent or other problems. When all is said and done a surgical discectomy remains the "gold standard" of care when performed by a qualified individual"

Warnke et al. did note: "We accept that it is widely acknowledged that removal of scar tissue produces new scarring. It is not clear whether the use of the thecaloscope can provide longer lasting relief but technical progress will hopefully give rise to better and more suitable instruments in the future...With regard to the therapeutic possibilities, further research is required."

As we have seen, the various types of attempts to reduce scar tissue, including endoscopic resection, will at best only have short-term benefit as the scar tissue tends to recur. In fact, these procedures may exacerbate the problem considerably and of course a procedure such as Racz, which uses such a toxic cocktail of injected agents, carries a risk of causing arachnoiditis.

EPIDUROLYSIS (RACZ)

Epidurolysis, pioneered by Dr. Gabor Racz, is used to dissolve scar tissue around trapped nerves in the epidural space: i.e. it reduces the amount of epidural fibrosis.

Scarring (adhesions) in the epidural (peridural/extradural) space is common after spinal surgery. It may be severe and cause symptomatic compression of nerve roots as they exit the spinal cord.

The epidurolysis involves injection of a mixture of local anaesthetic (lidocaine/bupivicaine), steroid (triamcinolone: Aristocort/Kenalog; methylprednisolone: depo-medrol/depo-medrone), X-ray contrast agent, the enzyme hyaluronidase (hyalase) and concentrated salt solution.

Hyaluronidase is a naturally-occurring enzyme that acts on hyaluronic acid, which is the "glue" that binds connective tissues together.

The procedure involves an injection of contrast agent into the epidural space in order to locate the scar tissue. Then an implanted catheter is used to deliver hyaluronidase safely and also to perform some mechanical lysis of the scar tissue.

Epidural steroid and local anaesthetic injections

At the American College of Rheumatology (ACR) 66th. Annual Meeting, October 2002([708]), Dr. Nigel Arden, a senior lecturer in rheumatology at the University of Southampton presented research on steroid injection for unilateral sciatica. Despite using the highest dose of the most potent steroid preparation (triamcinolone acetonide 80mg and bupivicaine) the study found that the procedure only provided limited relief and no sustained benefit. Dr. Arden admitted that in the UK the procedure is fairly common, "for every million population that comes into the hospital, we are doing 800 epidurals". He also conceded, "There is no quick fix or magic injection" and suggested that whilst pain consultants are keener on this form of treatment, "rheumatologists tend to think they do not work."

Dr. Antonio Aldrete has recently published a preliminary report ([709]) on the use of the non-steroidal anti-inflammatory indomethacin given epidurally instead of methylprednisolone in treating recurrent low back pain after surgery (post-laminectomy syndrome). Whilst the new drug was as effective as a normal dose of steroid (and was given in saline or local anaesthetic solution), the author noted that amongst the patients excluded from the study were those with arachnoiditis.

With respect to the risks involved in epidural steroid injections, O'Connor et al ([710]) sum up the situation by stating that the "abnormalities of the epidural and subarachnoid spaces in such patients" (i.e. with chronic spinal arachnoiditis)... give rise to "unpredictable and potentially dangerous results" following drug injection into these spaces.
Therefore this form of treatment has absolutely no place in a regime to manage arachnoiditis.

NERVE BLOCKADE

Sympathetic ganglion block: surgical, chemical and radiofrequency blocks have been used for many years, especially in the treatment of Reflex Sympathetic Dystrophy (RSD, now termed CRPS I, Complex regional pain syndrome Type I). Sympathectomy involves injection of local anaesthetic +/- steroid (e.g. prednisolone) into a ganglion, which is essentially a region where there is a collection of sympathetic nerves. One of these is the Stellate Ganglion, in the neck, which is sometimes blocked to relieve orofacial pain, such as trigeminal neuralgia. If pain is "sympathetically maintained" (SMP) then a nerve block might be able to temporarily relieve it; however, if it has spread and become centralised (i.e. originates in the central nervous system) then it is not amenable to this form of treatment: sympathetically independent pain (SIP) does NOT respond to nerve blockade. Sympathetic blockade may also be used to relieve circulatory problems such as Raynaud's or for treatment of hyperhidrosis (excessive sweating).

Somatic nerve block: peripheral nerve entrapment problems can lead to chronic pain in various parts of the body. Generally, these pains are termed "neuralgia". Examples include: occipital neuralgia (at the back of the head); abdominal cutaneous nerve entrapment syndrome (secondary to surgery/trauma/pregnancy); ilioinguinal nerve, linked to pelvic pain and has been successfully treated in women. ([711]) In trigeminal neuralgia (TGN), a procedure called rhizotomy may be carried out using glycerol, but repeats of this procedure are frequently unsuccessful in primary TGN. In TGN secondary to Multiple Sclerosis, the recurrence rate of pain is even higher.

'Permanent' Nerve Blocks:

Note: due to the plasticity of the nervous system, it is now recognised that nerve blocks are not permanent. Ethanol (alcohol) has been widely used in neurolytic procedures. Concentrations from 3-100% may be used. It destroys nerves by extracting cholesterol and other lipids (fats) and by protein precipitation. However, axonal regeneration is possible (unless the cell body is destroyed). High concentrations of alcohol (90-100%) may produce a chemical neuritis.

Phenol: Animal studies ([712]) show that phenol (carbolic acid) at 6% concentration causes local necrosis in 24 hours, complete degeneration by 45 days and regeneration in 75 days. Sensory recovery after phenol is faster than after alcohol.

The State of Colorado guidelines (xxv) state clearly, "**neuroablative procedures have no proven value in the treatment of nonmalignant chronic pain because of the high risk of developing a deafferentation pain syndrome."**

Hanekop et al ([713]) stated "The only neurolytic procedure which still has some importance is the neurolysis of the celiac ganglion for alleviation of pain in the upper abdomen mostly due to pancreatic cancer. This approach seems to be highly effective and tends to be afflicted with only minor complications. **Other neurolytic blocks have shown solely local and temporal efficacy. In their majority they are unprecise and often accompanied by severe complications**." They further commented: "Where suitable, the use of neurolytics is replaced by radiofrequency thermocoagulation, to a lesser degree by cryoanalgesia. Both procedures normally do not yield better analgesia, but do result in fewer complications."

Donner et al ([714]) wrote in 1998, "Repetitive nerve blocks as a monotherapeutic treatment are losing importance in the therapy of chronic pain."

Adverse effects of nerve blocks:

- Nerve damage: direct neurotoxicity from local anaesthetic, especially from preservatives such as sodium metabisulfite; mechanical trauma damage. Leakage from intended injection site.
- Vascular injury: puncture of blood vessels
- Pneumothorax (air in chest cavity)
- Other tissue trauma: kidney damage if lumbar area; bowel; etc.

- Dural puncture and direct intrathecal injection: note neurotoxicity of local anaesthetics; post-dural puncture headache: severe, sometimes treated with epidural blood patch which is highly irritant and can cause arachnoiditis.
- Backache
- Unintentional spread of local anaesthetic: epidural spread has been recorded with brachial plexus, facet joint injection and intercostal (between ribs) block. **This can be disastrous if it involves neurolytic agents.**

Systemic toxicity of local anaesthetics includes allergic reaction and cardiovascular effects such as heart arrhythmias. Common complaints include: tinnitus, light-headedness, metallic taste, numbness around the mouth: these occur at lower plasma levels such as 3-5 mcg/ml. More serious effects such as muscle twitching or decreased consciousness may signal the onset of seizures or coma. Risk of toxicity relates to: dose administered, vascularity (blood vessels) at the injection site, use of epinephrine in the preparation and the choice of drug (lidocaine is more toxic than bupivicaine) Injection sites near the head (such as stellate ganglion block) need to be performed with considerable care to avoid injection into blood vessels: as little as 2-3 ml of anaesthetic can precipitate a seizure.

Other problems with sympathetic blocks include changes in heart rate, pupil response to light/dark,(usually have small pupils) loss of sweating in the area served by the relevant nerve and/or increased sweating in other areas, changes in blood flow. Horner's syndrome may occur after a stellate ganglion block manifesting with a small pupil on the affected side, a droopy eye and loss of facial sweating.

Hongo et al. ([715]) looked at 41 patients treated with epidural neurolysis using 50 % ethyl alcohol 2 ml. 38 suffered from cancer pain and three patients were complaining of chronic benign pain. On average the block was repeated 2.3 times in each patient. Follow up in 30 of the patients revealed that 47% reported 70% or greater pain relief and 20% reported around 50% relief; duration of relief was on average 54 days. Notably some 43% of patients reported adverse effects, the most common of which was pain after the block was performed.

Radiofrequency Neurolysis (Ablation) (RF)

RF uses radiofrequency waves to shake up charged chemical particles (ions) within the nerves, thus producing heat, which is allowed to reach approximately twice the body temperature for 60-90 seconds. This technique appears to produce a longer-lasting pain relief than chemical nerve blockade, and there is not the risk of spread of the chemical.

Radio-frequency nerve blocks have been beneficial in the following conditions:

- Intractable back pain
- Headaches and facial pain, trigeminal neuralgia*
- Neck, arm and shoulder pain

- Chest wall pain
- CRPS

(* Percutaneous stereotactic radiofrequency rhizotomy PSR)

Some centres insist on selection criteria to include previous good response to local anaesthetic blocks.
The procedure tends to block nerve function for 6-9 months (may be only 3 months or up to 18 months)
It is performed under fluoroscopic control and does not require general anaesthetic.
Local anaesthetic is injected into the area as part of the procedure to ensure the correct nerve is being treated (and also to numb the tissues through which the RF needle is passed).

Dr. Gatell of the Atlanta Pain Relief Centre has used this technique. He warns "however, each individual case may not respond with 100% pain relief, and pain may recur or even become worse (Anesthesia Dolorosa). So RF is best reserved as a last resort in treating intractable chronic painful conditions that have not responded to optimal medical pain therapy."

Yoon et al. at the Walton Centre in Liverpool ([716]), conducted a retrospective analysis of long-term efficacy of percutaneous radiofrequency thermocoagulation of the trigeminal ganglion or root for the relief of trigeminal neuralgia. They looked at 81 cases. Initial success rate was 87%; the probability of remaining pain-free 1, 2 and 11 years after the procedure was 65, 49 and 26%, respectively. Patients who had typical symptoms and no previous surgery did best. Adverse events included dysaesthesia in 20 patients, corneal numbness in 12 patients and masseter weakness in 3 patients.

Dutch doctors in Maastricht ([717]), evaluated the use of radiofrequency for stellate ganglion blockade used in chronic pain syndromes in which the sympathetic nervous system is thought to be involved. They reviewed 86 RF-SG procedures and conducted a Medline literature review search on SG blockade. IN their clinic, they found that 39.5% of 221 patients who had received a prognostic SG block subsequently underwent RF-SG. 40.7% had a greater than 50% reduction in pain whilst 54.7% reported no improvement and 4.7% had worsened pain. Literature search revealed partial pain relief in 41.3% of patients, complete relief in 37.8% and no relief in 20.9%. They concluded: “Our retrospective study shows that an RF-SG block is most likely to be of benefit for patients suffering from complex regional pain syndrome type 2, ischemic pain, cervicobrachialgia, or postthoracotomy pain. Clinical efficacy remains to be proven in a randomized controlled trial, however.”

Botox: Botulinum toxin

Initially introduced as a treatment for squint (strabismus), Botox injection is now a widespread cosmetic treatment used to disperse signs of ageing. However, it has also been used to reduce symptoms in conditions such as torticollis, blepharospasm and spasticity and as a measure of pain relief when the pain is due to muscle spasm.
The microorganism Clostridium botulinum produces the toxin (BTX). Licensed products Dysport ® and Botox® type A toxins are licensed for blepharospasm, spasmodic torticollis and treatment of a foot deformity called equines which occurs in people with cerebral palsy from the age of 2 years. Botox® is also

licensed in places like Switzerland for treatment of lower leg spasticity in children with cerebral palsy aged 2-12 years and adults with acquired spasticity due to nervous system disorders including stroke.

The technique makes use of the neurotoxic properties of the botulism toxin, to paralyse local areas of muscles by its effect on the neurotransmitter acetylcholine. The result is a reduction in muscle contraction and a dose-dependent weakness and atrophy. The extent of denervation depends upon the dose and volume of the injection. The effect, which may be delayed initially, setting in 24-72 hours after injection, lasts 2-6 months, and is terminated by axon sprouting. However, this raises the question of abnormal sprouting which has been shown in the past to be implicated in severe pain after nerve block, due to sideways sprouting, causing *anaesthesia doloureux*. The weakness and muscle atrophy tend to resolve over 3-4 months during which time there is formation of new rudimentary nerve-muscle synapses, which then regress once the original neuromuscular junction has recovered. Obviously this means that injections need to be repeated to have a lasting effect.

Lang, at the Department of Rehabilitation Medicine, Emory University School of Medicine and Hospitals, Atlanta, USA, has written on the use of BTX in myofascial pain syndrome ([718]) and chronic pain syndrome ([719]). Lang suggests "the underlying problem in many types of muscle pain disorders is a distortion of critical structures that causes functional deficits and pain. An objective of treatment is to reverse this distortion, enabling repair of damaged tissues and strengthening of weakened muscles." BTX helps to reduce heightened muscle tone and overactivity, and may therefore be a useful part of an overall treatment approach that includes physical therapy to help restore normal muscle length and biomechanical balance to improve the prospect of ensuring long-term relief from associated pain.

Difazio and Jabbari recently suggested ([720]): "Botulinum toxin, which has already been shown to alleviate pain associated with cervical dystonia and other conditions characterized by muscle spasticity, is now being studied for the treatment of back pain. Preliminary evaluations have shown that this treatment is safe and has the advantage of providing local relief directly to the site of injury or pain, without causing systemic side effects. Initial data from small trials also suggest that botulinum toxin is effective, alleviating back pain in selected patients."

It is, however, important to remember that as yet, longer-term effects have not been evaluated and further research into safety and efficacy are needed.

Most adverse effects tend to be transient and localised and include: local muscle weakness, dysphagia (trouble swallowing), 'flu-like symptoms for up to a week, rash and brachial neuritis (the last is not self-limiting). Side –effects tend to peak at 2-4 weeks after the injection. The same dose and pattern of injections may produce variable results, so that side effects may occur despite trouble free injections in the past.

After repeated treatments, resistance due to antibodies to the toxin may develop. Longer-term consequences include muscle weakness and atrophy. Systemic adverse effects are unlikely but remain a possibility in certain vulnerable patients, so this form of treatment is relatively contraindicated in patients with neuromuscular disease.

Non-pharmacological treatments

These include:

STIMULATING TREATMENTS

Massage / muscle rubs

- These can be most helpful in relaxing tense or cramped muscles, especially if oil such as lavender is used as this has muscle relaxant properties.

Transcutaneous Electrical Nerve Stimulation:

Transcutaneous electrical nerve stimulation (TENS) is a commonly used form of electroanalgesia. Whilst there have been hundreds of clinical reports of the effective use of TENS for various types of conditions such as low back pain (LBP), myofascial and arthritic pain, sympathetically mediated pain, bladder incontinence, neurogenic pain, visceral pain, and postsurgical pain, many of these studies were uncontrolled, which has led to ongoing debate about how effective a treatment it really is.

TENS is thought to produce analgesia by a mechanism of the analgesia explained by the gate control theory proposed by Melzack and Wall in 1965. The gate usually is closed, inhibiting constant nociceptive transmission via C fibres from the periphery to the T cell. When painful peripheral stimulation occurs, the information carried by C fibres reaches the T cells and opens the gate, allowing pain transmission centrally to the thalamus and cortex, where it is interpreted as pain. The gate control theory postulated a mechanism by which the gate is closed again, preventing further central transmission of the nociceptive information to the cortex. The proposed mechanism for closing the gate is inhibition of the C-fibre nociception by impulses in activated myelinated fibres.

TENS is thought to produce neuromodulation by the following proposed mechanisms:

- Presynaptic inhibition in the dorsal horn of the spinal cord
- Endogenous pain control (via endorphins, enkephalins, and dynorphins)
- Direct inhibition of an abnormally excited nerve
- Restoration of afferent input

Laboratory studies suggest that electrical stimulation delivered by a TENS unit reduces pain through nociceptive inhibition at the presynaptic level in the dorsal horn, thus limiting its central transmission. The electrical stimuli on the skin preferentially activate low- threshold myelinated nerve fibres. The afferent input from these fibres inhibits propagation of nociception carried in the small unmyelinated C fibres by blocking transmission along these fibres to the target or T cells located in the substantia gelatinosa (laminae 2 and 3) of the dorsal horn.

A TENS unit consists of one or more electric signal generators, a battery, and 1 or 2 sets of electrodes. Stimuli have variable current strengths, pulse rates, and pulse widths. The preferred waveform is biphasic. The usual settings used clinically are:

- Amplitude - Current at low intensity, comfortable level, just above threshold
- Pulse width (duration) - 10-1000 microseconds
- Pulse rate (frequency) - 80-100 impulses per second (Hz); 0.5-10 Hz when stimulus intensity is set high

When used for pain control, it is best to try different frequencies and intensities to find the most effective combination. Optimal settings are subjective and tend to be determined by trial and error. Electrode positioning is an important factor and may require assistance from a helper. Usually, the electrodes are placed initially on the skin over the painful area, but other locations (e.g., over cutaneous nerves, trigger points, acupuncture sites) may actually be more effective.

There are 3 setting options:

1. Conventional: high stimulation frequency (40-150 Hz) and low intensity, just above threshold, with the current set between 10-30 mA. The pulse duration is short (up to 50 microseconds). Pain relief should be rapid and persist whilst the stimulus continues, but tends to diminish once the treatment is stopped. Patients tend to wear the TENS all day and turn it on for approximately 30-minute intervals throughout the day. For those who respond well, analgesia may persist for a variable time after the stimulation has stopped.
2. Acupuncture-type setting: the unit delivers low frequency stimulus trains at 1-10 Hz, at a high stimulus intensity, close to the tolerance limit of the patient. This may well be more effective but is often uncomfortable and therefore poorly tolerated. It may be worth trying in people who do not respond to conventional TENS treatment.
3. Pulsed (burst) TENS uses recurrent bursts at 1-2 Hz with a frequency of impulses within each burst of 100Hz. This is low-intensity stimulus with high frequency bursts. There has been no particular advantage established for this method.

The intensity of the impulse depends on both pulse duration and amplitude; the acupuncture-like method is less tolerable because the impulse intensity is higher. The level of current flow depends on impedance of electrodes, skin and tissues (skin impedance is reduced by application of electroconductive gel) and with repetitive stimulus, the skin impedance reduces, so that an increased current flow may occur as the stimulus continues. Skin irritation can occur in around a third of patients, often in part due to the conductive gel drying out. Self-adhesive disposable electrodes may be helpful and repositioning them slightly for repeated applications can reduce skin irritation.

Indications for TENS use:

- **Neurogenic pain** (e.g., deafferentation pain, phantom pain), sympathetically mediated pain, postherpetic neuralgia, trigeminal neuralgia, atypical facial pain, brachial plexus avulsion, pain after spinal cord injury (SCI)
- **Musculoskeletal pain:** including joint pain from rheumatoid arthritis and osteoarthritis. Use of TENS in chronic LBP and myofascial pain is controversial, as placebo-controlled studies fail to show statistically significant beneficial results.
- **Visceral pain and dysmenorrhoea**
- **Urge incontinence**
- **Angina pectoris**
- **Dental anaesthesia.**
- **Assist patients in regaining motor function following stroke**
- **To control nausea in patients on chemotherapy**

A recent Cochrane Review ([721]) on use of TENS in the treatment of chronic low back pain concluded:

"The results of the meta-analysis present no evidence to support the use of TENS in the treatment of chronic low back pain. Clinicians and researchers should consistently report the characteristics of the TENS device and the application techniques used. New trials on TENS should make use of standardized outcome measures. This meta-analysis lacked data on how TENS effectiveness is affected by four important factors: type of applications, site of application, treatment duration of TENS, optimal frequencies and intensities."

Contraindications for the use of TENS

- Should not be used in patients with a pacemaker (especially of the demand type).
- Should not be used in pregnancy (may induce premature labour).
- Should not be applied over the carotid sinuses due to the risk of acute hypotension through a vasovagal reflex.
- Should not be placed over the anterior neck because of possible laryngospasm due to laryngeal muscle contraction.
- The electrodes should not be placed in an area of sensory impairment where the possibility of burns exists.
- TENS should be used cautiously in patients with a spinal cord stimulator or intrathecal pump.

New techniques:

- **1. Interferential current therapy (IFC)** is based on summation of 2 alternating current signals of slightly different frequency. The resultant current consists of cyclical modulation of amplitude, based on the difference in frequency between the 2 signals. When the signals are in phase, they

stimulate, but no stimulation occurs when they are out of phase. The beat frequency of IFC is equal to the difference in the frequencies of the 2 signals. E.g. the beat frequency (stimulation rate) of a dual channel IFC unit with signals set at 4200 and 4100 Hz is 100 Hz. IFC therapy can deliver higher currents than TENS and can use 2, 4, or 6 applicators, arranged in either the same plane for use on regions such as the back or in different planes in complex regions (e.g., the shoulder).

- 2.**Percutaneous electrical nerve stimulation (PENS)** combines advantages of electro acupuncture and TENS. Instead of using surface electrodes, PENS uses acupuncture-like needle probes as electrodes, placed at dermatomal levels corresponding to local pathology. The main advantage of PENS over TENS is that it bypasses the local skin resistance and delivers electrical stimuli at the precisely desired level. In patients with chronic LBP and sciatica, PENS has been found to be more effective than TENS in providing short-term pain relief and improved function ([722]), including an improved quality of sleep and sense of well-being when used at 4 Hz. Ghoname et al. ([723]) found that the frequency of electrical stimulation is an important determinant of the analgesic response. 40% of their patients reported that 15/30 Hz was the most desirable therapy, and it was also more effective in improving the patient's sense of well being. Alternating stimulation at 15-Hz and 30-Hzfrequencies was more effective than either 4 Hz or 100 Hz. PENS has also been used successfully in patients with herpes zoster (shingles), headache ([724]) and cancer with bony metastases.

Acupuncture: contact with patients who have tried this suggests that it is not as useful as could be hoped although some individuals do gain relief.
Beppu et al. ([725]) reported on the use of meridian acupuncture (alone or combined with moxibustion) on trigeminal neuralgia. Treatments were repeated 2-4 times a month. The authors found "Five patients were restored to a pain-free state. The other five patients noted a decrease in pain, but with some level of pain remaining (significant pain in one patient)." They concluded that acupuncture was a useful treatment.

The World Health Organisation (WHO) lists a variety of medical condition that may benefit from treatment with acupuncture with or without moxibustion. These include prevention and treatment of nausea and vomiting; treatment of pain and addictions to alcohol, tobacco and other drugs; treatment of pulmonary problems and rehabilitation from neurological damage such as that caused by stroke. However, screening by doctors to ascertain suitability for acupuncture treatment is recommended.

The British Medical Acupuncture Society (BMAS) London Teaching Clinic at the Royal London Homeopathic Hospital lists the following indications for acupuncture: ([726])

Primary myofascial pain
Pain from skeletal muscle; localised tender knot of muscle may have a wide pain referral pattern; frequently affects neck, shoulder girdle and hip girdle; this responds very well to direct trigger point needling.

Nociceptive musculoskeletal pain

- Osteoarthritis (especially knee, ankle, acromio-clavicular joint & cervical spine)
- Achilles tendonitis, lateral & medial epicondylitis (elbow pain)

Functional, recurrent & other disorders

- Irritable bladder symptoms (nocturia, frequency & urgency)
- Irritable bowel syndrome
- Migraine headaches
- Dry eyes and xerostomia
- Menstrual & menopausal symptoms (especially hot flushes)

Allergies

Hayfever, allergic rhinitis, some forms of urticaria.

Skin

Local acupuncture needling can be useful in the treatment of localised rashes and ulceration, whereas generalised chronic skin diseases are less likely to respond, although those with an allergic component (some forms of eczema) may do well. Acupuncture seems to be effective in treating itch.

Fibromyalgia

One randomised controlled trial of high quality found a specific effect of electroacupuncture in fibromyalgia. In practice this condition is not easy to treat, but associated myofascial pain often responds well.

Neuropathic pain

"Neuropathic pain is difficult to treat. Acupuncture will occasionally have dramatic effects, but often will do nothing for these conditions."

Belgrade ([727]) notes: "Stimulation-based therapies (e.g., transcutaneous electrical nerve stimulation, acupuncture, spinal stimulation, massage) can help in cases of neuropathic pain. However, occasionally these methods aggravate symptoms, especially when allodynia is present. In these cases, stimulation of adjacent uninvolved dermatomes may be effective.**"**

Acupuncture is also known as 'dry needling'.

Resteghini ([728]) discusses published medical literature on acupuncture:

Tulder (1997) conducted a systematic review of randomised controlled trials of common treatment for back pain, including acupuncture. He concluded that the trials had poor methodology. There is however, some evidence to suggest that acupuncture is effective.

Gunn (1980) looked at dry needling in patients with chronic low back and found that they did better than controls. Garvey (1989) compared dry needling with local anaesthetic injection in patients with low back

pain, and found that there was a 63% improvement rate with dry needling. Hong (1994) also supported the use of dry needling as opposed to injection of trigger points.

Acupuncture has been used in Asia for thousands of years for a side variety of pain conditions, especially the chronic type.
In neuropathic pain the aim of acupuncture is to restore supersensitive structures to normal, rather than to provide pain relief.

How does acupuncture work?

Traditional theory suggests that acupuncture regulates the flow of Qi (life force), restoring a balance by moving it to areas where it is deficient and draining it from where it is in excess.
There is an important paradox in which localised acupuncture can produce analgesia in distant areas of the body. This is called the nonsegmental analgesic effect. It is thought to arise due to generalized neurohormonal mechanisms, involving the release of free (-endorphin and apparently also of met-enkephalin, and by two descending neuronal mechanisms, the first of which is serotonergic and the second adrenergic. A third descending system (diffuse noxious inhibitory controls) may also contribute in a minor way to the acupuncture effect.
When a needle is inserted into a tender area, it tends to initiate a lasting reduction in tenderness in the local area: this is the segmental effect. Segmental acupuncture operates through a circuit involving inhibitory enkephalinergic stalked cells in the outer part of lamina II of the spinal grey matter, which are directly contacted by group II primary afferents. In addition, there is a considerable body of evidence implicating the sympathetic system effects.

Possible course of events after acupuncture

Commonly after the initial treatment there is a fairly transient improvement, lasting 2 to 3 days.
Subsequent treatments may provide longer periods of remission, which may also be if greater therapeutic effect. The ideal aim is for total remission of symptoms after 3-6 treatments, but often relief may only be partial and symptoms may recur, necessitating further treatment at intervals.
It is also common for patients to experience an aggravation of existing symptoms that rarely lasts more than 2 or 3 days, although occasionally it may last longer. The occurrence of an aggravation tends to suggest that there will be a later therapeutic response but this is not always the case.

IntraMuscular Stimulation

Intramuscular Stimulation (IMS) is a system of diagnosis, physical analysis, and treatment of myofascial pain syndromes and chronic pain of neuropathic origin, based on acupuncture principles.
IMS was developed by Dr. Chan Gunn, a clinic physician at the Workers' Compensation Board of British Columbia. Dr. Gunn is now a clinical professor teaching IMS at the University of Washington's

Multidisciplinary Pain Centre in Seattle and University of British Columbia's Medical School. IMS is also taught and utilised at many other pain centres around the world.

A very thin acupuncture needle is used, which is painless in normal muscle, but in supersensitive, shortened muscle, causes a discomfort similar to a muscle cramp, due to the muscle contracting around the needle. In fact, this is a good sign, as it tends to precede a release of the muscle tension.

The effects of IMS are cumulative— dry needling is thought to stimulate healing.

Treatments are usually once a week, the number of treatments required depends on several factors: the duration and extent of the condition; how much scar tissue there is, and how quickly the body can heal. In published studies of patients with non-specific low back pain, the average number of IMS treatments required was 8.2. More may well be needed in arachnoiditis due to the complexity of the condition.

The goal of treatment is to release muscle shortening which presses on and irritates the affected nerves.

Physiotherapy: must be gentle as vigorous exercise may precipitate a flare-up. As in conditions such as Multiple Sclerosis, a non-fatiguing programme is likely to be the most beneficial. However, even during a flare-up, maintaining mobility is vital. Range of movement exercises ensure that joints remain as supple as possible and help to reduce muscle spasm. Graded gentle increase in exercise capacity can be a helpful strategy to improve mobility, to enhance circulation and to reduce muscle spasm. Dr. Paul Watson, the first physiotherapy consultant in the UK and a Senior Lecturer at the University of Leicester Medical School, has a special interest in chronic back pain. Is it safe to exercise? Dr. Watson's view at a meeting of the Pain Society in London in Autumn, 2002 is that it is, provided that the body is structurally sound. Exercise reduces heart disease and stress illnesses. However, Dr. Watson noted that in the case of neuropathic pain such as that experienced in arachnoiditis, the **pain must be well controlled pharmacologically for exercise to be feasible**. He suggested that patients with this type of pain require slow desensitisation of the nervous system, which means a far longer time frame than other types of pain. Individual rather than group therapy over 1-2 years may well be necessary, although it may not ultimately involve more overall hours than the standard pain management programme (PMP) alongside work with a psychologist.

When there is central pain, conventional physiotherapy involving phasic stimulation of the skin may trigger burning pain by creating skin friction and stimulating gamma pain (see above under central pain); the aim should be muscle stretch using a technique which moves the muscle without rubbing the skin. However, this deep massage takes considerable time. The optimum may be to have 20 minutes of deep massage a day just prior to performing whatever necessary tasks the patient wishes to tackle.

Hydrotherapy: often very useful, but the water must not be too warm (heat intolerance is common in arachnoiditis patients)

Foot care: as with all cases of peripheral neuropathy causing loss of sensation in the feet, vigilance and early treatment of skin abrasions/damage/infection is essential. Close attention to the suitability of footwear etc. is important.

MIND-BODY TECHNIQUES:

Astin et al. ([729]) noted:

"Drawing principally from systematic reviews and meta-analyses, there is considerable evidence of efficacy for several mind-body therapies in the treatment of coronary artery disease (e.g., cardiac rehabilitation), headaches, insomnia, incontinence, chronic low back pain, disease and treatment-related symptoms of cancer, and improving postsurgical outcomes."

Zelter et al. ([730]) looked at a complementary and alternative medicine (CAM) package combining acupuncture and hypnosis for chronic paediatric pain. They reported: "Both parents and children reported significant improvements in children's pain and interference following treatment."

Nielson and Weir ([731]) looked at multimodal biopsychosocial treatments that include cognitive-behavioural components, studying three systematic reviews of the literature and 21 randomized controlled trials. They found that these treatments "are effective for chronic low back pain and other musculoskeletal pain for up to 12 months (level 2)," and concluded: "Future studies of cognitive-behavioral treatments should be condition specific, rather than include patients with different pain conditions to provide the evidence for this review."

Hypnosis:

In 1995, a panel convened by the United States National Institute of Health (NIH) found that behavioural treatment and relaxation therapies were helpful in chronic pain and insomnia.

The group stated that there was evidence that hypnosis is effective in alleviating chronic pain associated with various cancers. They also found strong evidence that relaxation approaches are effective in treating a variety of chronic pain conditions such as low back pain, arthritis, and headache.

> "The role of hypnosis in treating chronic pain patients is uncertain. Some studies have shown that 15 to 20 percent of hypnotizable patients with moderate to severe pain can achieve total relief with hypnosis. Other studies report that hypnosis reduces anxiety and depression. By lowering the burden of emotional suffering, pain may become more bearable." ([732])

The American Cancer Society, in their Guide to Complementary and Alternative Methods in 2000, noted:

"According to a report from the NIH, there is strong evidence that hypnosis can relieve some pain associated with cancer."

Cognitive Behavioural Techniques: these do not combat the pain directly, but are helpful in providing a range of co strategies. Implementation of these techniques takes a while to become effective. CBT is

used to target the range and level of activity, independence, use of healthcare and possibly (indirectly) pain itself. Behavioural methods may include goal setting and pacing, use of cues and consequences, relaxation applied to rest and activity, and reduction of medication. Cognitive and emotional change may be effected via education, challenging thought patterns and beliefs and working on attention control (the latter not just by distraction, there are other more sophisticated techniques). These address issues such as pain distress, depression and fear about what the pain means, frustration, and control.

The 1995 NIH panel found CBT to be: "moderately effective in altering pain intensity."

Common misconceptions about CBT:

Behaviour change is NOT:

- Telling the family to ignore the patient as if social support is disabling
- Assuming secondary gain

Cognitive change is NOT:

- Recommending coping strategies
- Correcting irrational thinking: the patient is neither stupid nor illogical if one looks at the premise from which he/she is working
- Simple distraction
- Dealing with beliefs without mobilising emotions (simply talking dispassionately won't help)
- Not implying that thinking the right thought can close the pain gate!

Relaxation/meditation: these are all helpful adjuncts to drug treatment, but few patients can manage on these pain management techniques solely.
Relaxation techniques involve the practice of two basic components: a repetitive focus on a word, sound, prayer, phrase, or muscular activity, and allowing oneself to neither fight nor focus on intruding thoughts. Done properly, relaxation therapy can lower breathing rate, heart rate, and blood pressure.
The 1995 NIH report found that relaxation is a useful adjunct in patients with chronic pain or insomnia.

Experimental treatments

Memantine hydrochloride, an NMDA antagonist, was launched in Germany by Merz in 1989 for the treatment of dementia, and is now under development for use in treating neuropathic pain. The manufacturers are in the process of applying for license for this use both in the UK and the US.

Amantadine generally used to treat symptoms of Parkinson's disease. It has also been reported ([733]) to be effective in managing neuropathic pain (in three patients, acute administration resulted in complete resolution of symptoms, which was attributed to termination of the "wind-up" mechanism). Pud et al ([734]) looked at intravenous administration of amantadine for relief of cancer-related neuropathic pain and found that there are indications that suggest it may be of benefit, but they recommend further trials. It is, in fact, also an antiviral agent; it is known to be helpful in relieving muscle stiffness and tremor in neurological conditions such as Parkinson's. It is also well established to treat fatigue and reduced exercise tolerance in Multiple Sclerosis.

Ngf The completed trial of nerve growth factor (ACTG 291) has been reported in *Neurology 2000; 54:1080-1088.* NGF did provide significant relief to pain in patients with neuropathy based on Gracely Pain Scale scores. However, during the 18-week trial, quantitative sensory testing did not document return of function in the peripheral nerves.

Intrathecal adenosine: has been found to reduce areas of mechanical hypersensitivity and provides analgesia in patients with neuropathic pain. Experimental studies ([735]) show that the higher doses cause side effects which can be avoided by a lower dose that is just as effective.

Combined morphine and magnesium: Magnesium is a natural NMDA antagonist occurring in the spinal cord. A recent animal study ([736]) has found that combining morphine (0.1 mg/kg) and magnesium sulfate (125 mg/kg) in rats with mononeuropathy, "exerted a significant anti-allodynic effect". A clinical study of patients receiving spinal analgesia for labour, the addition of magnesium sulfate to the opioid fentanyl prolonged analgesia with no demonstrated increase of side effects.([737])

Magnesium hydroxide (300-600mg a day) with malic acid (1200-1400mg a day) gave significant pain relief to fibromyalgia patients within 48 hours in clinical trials.

Calcium channel blockers: nifedipine, verapamil etc. have been investigated in animal studies and found to potentiate the effects of opiates. ([738]) in 1995, Romanian article ([739]) discussed the clinical effects of calcium channel blockers in enhancing the analgesic effects of aspirin and paracetamol.

Cannabinoids: As Beaulieu and Rice recently stated ([740]), "The cannabinoid system is a major target in the treatment of pain".

In 1997, reviewing a series of trials in 1997, the U.S. Society for Neuroscience concluded that "substances similar to or derived from marijuana ... could benefit the more than 97 million Americans who experience some form of pain each year." ([741]) In the same year, National Institutes of Health in the USA published a "Workshop on the Medical Utility of Marijuana: Report to the Director," in Washington, D.C. ([742]) in which it was noted, "Neuropathic pain represents a treatment problem for which currently available analgesics are, at best, marginally

effective. Since delta-9-THC is not acting by the same mechanism as either opioids or NSAIDS [nonsteroidal anti-inflammatory drugs], it may be useful in this inadequately treated type of pain."

Authors of the 1999 Institute of Medicine (IOM) report, "Marijuana as Medicine: Assessing the Science Base," ([743]) described 3 types of pain that may be ameliorated by cannabinoids: somatic pain, visceral pain, and neuropathic pain. The researchers concluded that cannabinoids reduce painful stimuli to an extent comparable to opiates in potency and efficacy. "In conclusion, the available evidence from animal and human studies indicate that cannabinoids can have a substantial analgesic effect."

A 1998 University of California rat study ([744]) explained that THC, one of the active constituents of cannabis, affects circuitry at the base of the brain, modulating pain signals in a similar way to opiates. The authors concluded, "These results show that analgesia produced by cannabinoids and opioids involves similar brain stem circuitry and that cannabinoids are indeed centrally acting analgesics with a new mechanism of action."

Another component, anandamide, had also been found to produce effects in the pain-processing areas of the brain and spinal cord that appear to ease the sensation of pain. Rats in an Italian study ([745]) treated with a synthetic agent that blocked the action of anandamide demonstrated a longer and greater reaction to pain. Also, anandamide in conjunction with the endogenous compound PEA (Palmitylethanolamide) has been observed to reduced pain 100-fold. ([746])

Cannabis has been found to be effective not only in pain associated with various conditions, including multiple sclerosis and spinal cord injury, but also other symptoms associated with these conditions, such as muscle spasms and spasticity. A 1986 study ([747]) of 5patients with traumatic paraplegia found the administration of delta-9-tetrahydrocannabinol (THC) "clinically beneficial" in two patients, controlling their previously intractable spasticity. In 1990, Swiss neurologists reported ([748]) on the treatment of a paraplegic patient suffering from spasticity and painful spasms in his leg following spinal cord injury. A double-blind study was performed comparing 5 mg of THC, 50 mg of codeine, and a placebo. Delta-9-THC and codeine both had an analgesic effect in comparison with placebo, but only delta-9-THC showed a significant beneficial effect on spasticity.

The IOM report (see above) noted: "There are numerous anecdotal reports that marijuana can relieve the spasticity associated with ... spinal cord injury, and animal studies have shown that cannabinoids affect motor areas in the brain - areas that might influence spasticity."

In1998, a review article by Growing et al. ([749]) noted that the distribution of cannabinoid receptors in the brain suggests that they may play a role in movement control. The authors hypothesized that cannabinoids might modify the autoimmune cause of Multiple Sclerosis, and thus may both relieve symptoms of MS and retard its progression. A survey in 1997 ([750]) in the UK and US found that 30-97% of people with MS who smoked cannabis experienced relief in symptoms such as spasticity, chronic pain of extremities, acute paroxysmal phenomenon, tremor, emotional dysfunction, anorexia/weight loss, fatigue states, double vision, sexual dysfunction, bowel and bladder dysfunctions, vision dimness, dysfunctions of walking and balance, and memory loss (in descending order).

Various studies are currently underway in the UK, mostly involving patients with MS, although a few chronic pain patients are now being included.

GW Pharmaceuticals plc is developing non-smoked cannabis –based preparations and have been conducting clinical trials at Phase III level. In the November 5th. 2002 Press Release, the company stated that each of 4 randomised, double-blind, placebo-controlled trials using whole plant medicinal cannabis extract in patients with Multiple Sclerosis and neuropathic pain has reported positive data. There had been significant reductions in neuropathic pain, spasticity and sleep disturbance.

The GW product, Sativex®, is a whole plant medicinal cannabis extract containing Tetranabinex™ extract (tetrahydrocannabinol, THC) and Nabidiolex™ extract (cannabidiol, CBD) as its principal components. At the end of March 2003, GW submitted its regulatory dossier for Sativex to the UK regulatory authority, the recently renamed Medicines and Healthcare Products Regulatory Agency (MHRA), for an authorisation to market the product in two therapeutic indications:

- relief of symptoms in patients with Multiple Sclerosis
- relief of Neuropathic Pain (nerve-damage pain).

Subject to UK regulatory approval, GW aims to make Sativex available on prescription in the UK by the end of 2003.

GW is using three drug delivery technologies in the development of its products, specifically:

- Sub-lingual (under the tongue) spray - This technology is being utilised for the Group's lead product, which is now in Phase III trials. The spray pump is already approved by the Medicines Control Agency (MCA) in the UK and similar agencies elsewhere for use with specific medicines.
- Sub-lingual tablet - These tablets, which are intended to dissolve under the tongue rather than be swallowed by patients, have been developed in-house by GW and have been used in one of the Group's Phase II trials.
- Inhaler - GW is developing an innovative inhalation device for the delivery of its medicines, aiming to enable patients to benefit from the rapid relief associated with inhaled delivery but without exposure to the carcinogens produced when cannabis is smoked.

CAM TREATMENTS

CAM (Complementary and Alternative Medicine) has yet to be formally investigated in the specific setting of arachnoiditis, although Aldrete is undertaking a study on alpha lipoic acid and magnesium. However, by looking at some of the treatments that have proved effective in similar conditions such as diabetic neuropathy, we may be able to establish a useful regime.

Alpha Lipoic Acid

In the March 1997 Diabetes Care Journal the suggested oral treatment was alpha-lipoic acid 800-1000 mg a day for the treatment of peripheral neuropathy.

In Germany, where herbal treatment is much more prominent than in the UK and is widely accepted, conditions such as diabetic neuropathy are treated with ALA. In 1999, Ziegler et al ([751]) reported results

from a 3-week pilot study using 1800 mg a day ALA. They also found that oral treatment for 4-7 months tended to reduce neuropathic deficits and improved cardiac autonomic neuropathy.

Ruhnau et al. ([752]) reported, "oral treatment with 600 mg of TA t.i.d. for 3 weeks may improve symptoms and deficits resulting from polyneuropathy in Type 2 diabetic patients, without causing significant adverse reactions."

In 2000, Hilz et al ([753]) stated, "Symptomatic therapy includes alpha-lipoic acid treatment, as the antioxidant seems to improve neuropathic symptoms." They also advocated use of ALA alongside 'conventional analgesia', with evening primrose oil (EPO), containing gamma-linolenic acid (GLA), to improve nerve conduction velocities, temperature perception, muscle strength, tendon reflexes and sensory function.

Halat and Dennehy looked at the medical literature up to 2001 ([754]) and concluded: "Evening primrose oil, alpha-lipoic acid, and capsaicin have received the greatest attention for their use in diabetic neuropathy, but further studies are needed to confirm their efficacy. Patients using these products need to be informed of potential drug interactions and side effects."

The SYDNEY trial group, at Russian Medical Academy for Advanced Studies, Moscow ([755]), looked at the use of ALA in diabetic neuropathy. They concluded: "Intravenous racemic ALA, a potent antioxidant, rapidly and to a significant and meaningful degree, improved such positive neuropathic sensory symptoms as pain and several other neuropathic end points. This improvement of symptoms was attributed to improved nerve pathophysiology, not to increased nerve fiber degeneration. Because of its safety profile and its effect on positive neuropathic sensory symptoms and other neuropathic end points, this drug appears to be a useful ancillary treatment for the symptoms of diabetic polyneuropathy."

Femiano and Scully ([756]) have also found that ALA is beneficial in cases of burning mouth syndrome.

Red cell shape: Simpson has performed analysis of the shape of red blood cells, based on his previous work on patients suffering from Myalgic Encephalitis (ME) or fibromyalgia ([757]). He has found that, as in those other conditions, there is an increase in the number of flat red cells (normally they are biconcave discs). This phenomenon has considerable bearing on symptoms such as fatigue, as the flat cells have a reduced oxygen-carrying capacity and thus the increased need for energy in muscles during exercise is not met and the individual will fatigue much quicker than a healthy individual.

Evening Primrose Oil (EPO)

The use of Evening Primrose Oil to counteract symptoms is based on studies which have demonstrated that EPO induces improvement in blood flow and oxygen delivery to tissues, including nerve tissues in diabetic individuals (studied in rats): thus preventing or improving nerve conduction deficits. There will also be a benefit in the blood supply to muscles, which could impact on fatigue as well as muscle disturbances such as spasm.

As the Simpson and Anderson paper states: "There is strong anecdotal evidence for the effectiveness of EPO in relieving the symptoms experienced in many chronic conditions where such symptoms appear to be related to oxygen deprivation."([758])

In addition, there has been a Japanese study, which used lipoprostaglandin (Lipo PGE-1) to treat the pain of spinal stenosis and was shown to increase blood flow to the affected nerve roots and cauda equina, for a limited period. ([759])

EPO is converted in the body to Prostaglandin E-1, so it is reasonable to expect a similar effect. Indeed, PGE-1 has been shown to benefit patients with Raynaud's phenomenon, where spasm of the small blood vessels in the extremities results in poor circulation.

PGE-1 has also been shown to have a beneficial effect on red cell deformability. This brings us back to the abnormalities of red blood cells, observed by Dr. Simpson.

In Part 2 of Simpson and Anderson's study ([760]), 46 of the original 69 respondents participated in assessing the value of Evening Primrose Oil (EPO) as a dietary supplement for relief of symptoms experienced by arachnoiditis sufferers.

33 respondents trialled EPO but only 19 were taking the supplement at the end of the study. This was due to 6 discontinuing due to unacceptable side effects (predominantly gastrointestinal e.g. nausea/vomiting, diarrhoea, acid reflux, abdominal distension, with also one case of weight gain and one of facial swelling). A further 5 respondents felt that they gained no benefit and had therefore stopped taking EPO.

15 of the respondents tried 2 different products: of which 9 found one to be distinctly superior. However, the paper states, "No particular product appeared to stand out as superior to others. The effectiveness of any product appeared to be an individual response."

Dosage ranged from 1,000 to 5,000mg (4,000 being the recommended dose.)

Positive experiences with EPO included:

- Improved energy (12 subjects)
- Improvement in pain (slight to considerable in 12)
- Reduced muscle disturbances, particularly morning stiffness (10)
- Headaches reduced (6)

Subjects also reported: greater alertness, better quality of sleep and general improvement of wellbeing.

The paper ([761]) concluded that a recommended daily dose of Evening primrose oil of 4,000mg (4g) may exert a beneficial effect and improve some of the diverse symptoms of arachnoiditis.

However, further research is needed into this and many other aspects of a condition which has no specific pattern of presentation, and may indeed be labelled as one of the similar conditions: MS, ME, FM (fibromyalgia) or Lupus.

The authors also mentioned that the factors* predisposing to the condition and statistics on the prevalence of the condition remain unknown at this time.

(* NOTE: these are biological factors within the individual, which, when the body is challenged by extraneous risk factors such as trauma or chemical insult, interact to result in this incurable condition.

Recognition of these factors might help to determine who in the population is at greater than average risk of developing arachnoiditis from a procedure such as surgery/epidural injection.
These factors may be genetic, biochemical or mechanical, and may involve an autoimmune component.

As the authors state: "Ideally every person with disabling arachnoiditis should be referred to a spinal unit for inpatient rehabilitation, aiming for maximum function through pain management, occupational therapy and physiotherapy etc., followed by regular monitoring."

Note: Use of EPO or any other dietary supplement should be viewed as part of a holistic approach to treating arachnoiditis, which is a complex condition which is likely to respond best to a range of therapeutic interventions including pain relief, physical treatments, lifestyle changes, psychological techniques and participation in support groups.

GLA

Gamma linolenic acid is an Omega-6 fatty acid. It can be found in products such as Evening Primrose Oil (EPO), Borage Oil and Starflower Oil. GLA has been found to be beneficial in a number of conditions, most relevantly, Multiple Sclerosis and arthritis.
EPO takes about 8-10 weeks to start having an effect. Fang ([762]) demonstrated the effectiveness of GLA in providing arachidonate as raw material for the production of prostacyclin, and also stimulates COX-1 expression in some tissues.
Cameron ([763]) showed that a novel essential fatty acid derivative ascorbyl-GLA was 40 times as effective as GLA as a treatment for neuropathy. It is not as yet available commercially, but the same study showed that GLA plus ascorbate was over 75% as efficacious as ascorbyl-GLA. It may therefore be helpful to take a good dose of vitamin C along with the EPO. Nerve conduction and perfusion deficits in diabetic rats have been corrected by a combination of antioxidant and gamma-linolenic acid (GLA) supplements. This suggests a synergistic effect of antioxidant and GLA when used to combat diabetic neuropathy.
Other studies have shown that a combination of Omega-3 oils (in fish oils and flax oil) with Omega-6 has a significant benefit compared with the use of either type of oil alone.
A 1.3:1 GLA: alpha-lipoic acid ratio appears to be optimal against experimental diabetic neuropathy. (Cameron 1998[764])

Omega-3 Oils

Essential fatty acids EPA and DHA derived from fish oils have been found beneficial in conditions in which there is an inflammatory component. The old wives' remedy of cod liver oil does seem to have some rational basis and can be demonstrated scientifically to reduce symptoms in arthritis. Fish oils, whilst much slower to work, can be as effective as NSAIDs in the medium to long term in reducing joint pain. Dr. Robert Atkins, founder of the Atkins Centre in New York, and a renowned expert in integrated medicine, advocates the use of high dose EPA and DHA to combat autoimmune conditions. He has found that patients with conditions such as lupus, Crohn's disease and Multiple Sclerosis have benefited from this form of therapy.

A comparative study ([765]) looked at the effect of dietary supplementation with fish oil on the sciatic nerve of diabetic rats. Nerve conduction velocity was found to improve using the fish oil treatment, which also had a preventive effect on nerve damage. These data suggest that fish oil therapy may be effective in the prevention of diabetic neuropathy

Nutritional Strategy for Lowering PGE2:

A South African study in 1995 found that **fish oil and evening primrose oil** supplementation had biochemical results indicative of a favourable effect on osteoporosis. Evening primrose oil may have potentiated the effects of fish oil.

High intakes of fish, black currant, evening primrose, and borage oils may help optimize bone modelling and remodelling. Doses: 2 g per day of fish oil, evening primrose, or black currant or borage oil are safe, and may enhance bone formation, especially when used on a long-term, preventative basis.

Acetyl L-carnitine:

This amino acid is currently being investigated in the treatment of peripheral neuropathy. A randomized, controlled clinical trial in 1995 ([766]) demonstrated "a significant amelioration of symptoms" when patients took 2 x 500mg ALC (intramuscular injection) per day. (Note: The absorption of ALC taken orally is unlikely to be equivalent to the absorption of injectable ALC). A 1998 study by doctors in London noted that treatment with ALC may be one of the newer agents that could assist in the treatment of drug-induced peripheral neuropathy ([767]). Rat studies have shown that ALC attenuates nerve damage and promotes regeneration.([768]) A 1998 study at the Nagoya University School of Medicine in Japan showed that carnitine deficiency was closely related to the pathogenesis of diabetic neuropathy, leading the doctors involved to conclude that ALC holds considerable potential for the treatment of this type of neuropathy ([769]).

Herbal treatments: some arachnoiditis patients have tried various herbal preparations with different degrees of success; for instance, St. John's Wort, which acts similarly to Prozac, may be helpful in mild depression. *Please note: it is vital to check with your doctor and/or pharmacist before taking herbal preparations in case they interact with medication you are currently taking.*

Bromelain: reduces production of fibrin in the body; used in Germany to manage arthritis. ((Up to 3 250-300mg tablets four times a day (maxium effect take between meals): do not use if allergic to bee venom or if have high blood pressure or bleeding disorder.))

Uva Ursi: for unstable bladder; contains arbutin and hydroquinone (the latter has powerful antimicrobial activity): helps to strengthen muscles of bladder and is an effective remedy for UTIs. 100mg x2 for cystitis; restrict to 14 days. Bioforce Uva Ursi Complex tincture 15-20 drops three times a day. Do not use if pregnant or kidney disorder. DO not use for prolonged periods. Do not mix with fruit juice or vitamin C.

Further details on various herbs are available in "WHOA: Wholistic Treatment of Arachnoiditis"

Possible supplement regime

Vitamin A

Vitamin C 1-2 g

Vitamin E 400iu

Alpha-lipoic acid (thioctic acid) 100mg - 600mg

Vitamin B Complex

Magnesium (*Note: Excessive magnesium intake can cause renal problems)*

Zinc

MSM 1-2 g a day

Fish oil or flax oil capsules (high strength)

Evening primrose oil/ borage/starflower

Glucosamine for joint pains (+/- chondroitin)

Ginger/bromelain as anti-inflammatory

Gingko Biloba extract 120mg unless on NSAIDs or Warfarin

Note: Bromelain, an enzyme derived from pineapple, reduces fibrin

For further details please see "WHOA: a Wholistic Approach to Arachnoiditis" available from The Arachnoiditis Support Group, Knowsley.

Lifestyle measures:

- Pacing
- Reducing stressors
- Planning
- Adapting
- Stopping smoking (which is linked with poor healing and may reduce blood supply to discs by up to 70%)
- Avoiding excess alcohol

TREATMENT OF RELATED PROBLEMS:

Specialist assessment and treatment may be needed for problems such as bladder and bowel dysfunction. Management of urinary incontinence may include the use if drugs such as oxybutinin.

TREATING BLADDER PROBLEMS

As we have seen, various medications can affect bladder function.

Below are some of the pharmacological strategies for different bladder dysfunction. Further details are available in a separate article.

Overactive bladder:

anticholinergic drugs: such as Oxybutinin: Cystrin / Ditropan (now available in slow-release form: Ditropan XL); typical dose of Ditropan is 5mg 2-3 times a day. Ditropan XL is taken once a day, and may have a beneficial effect after about a week. Note that antidepressants such as amitriptyline and imipramine, which may be prescribed as adjuvant analgesics or for depression, have anticholinergic properties, so may be beneficial in reducing bladder instability. Anticholinergics act by blocking the passage of nerve signals through the spinal nerves. However, their effects are non-specific and can result in a variety of side-effects: the one which causes most patients to discontinue treatment is dry mouth, which can be quite unpleasant, but managed by chewing sugar-free gum. Other effects include constipation, blurred vision, nausea, drowsiness, confusion and weight gain. These drugs are not suitable for patients with cardiac problems, as they may cause abnormalities in heart rhythm. Patients with glaucoma (closed-angle type) should not be treated with anticholinergics, nor should those with obstructive urinary tract disorders. Oxybutinin was the 'gold standard' drug for 25 years or more. Reports suggest that there is subjective improvement in 50-80% of patients with detrusor instability, but some specialists maintain that there is only 40% objective urodynamic improvement, and that up to half the patients discontinue treatment due to dry mouth. The new slow release preparation was brought out in the United States in 1999, but was more recently approved for use in the UK. It appears that the drug is absorbed in the large intestine rather than the stomach so that side-effects may be reduced. Propantheline bromide (Probanthine) is another similar antispasmodic drug. Doses range between 15 and 30mg every 6-8 hours, but it has a very high side-effect profile, so is now considered as a low-priority second-line choice.

Tolterodine (Detrusitol) is a new drug, which is a muscarinic (cholinergic) receptor antagonist: that is, it blocks the effect of neurotransmitters, which act on receptors that control bladder contraction and salivation. Typical dose is 1-2 mg twice a day. Side-effects include, as expected, dry mouth; the drug cannot be used in people with urinary retention, gastric retention or glaucoma. However, the drug is more bladder-selective than other similar drugs, and whilst it is as effective as oxybutinin, the incidence of severe dry mouth is lower.

Hyoscyamine sulfate (Levbid, Cytospaz): an anticholinergic; contra-indicated for obstructive disorders, in patients with glaucoma and ulcerative colitis.

Dicyclomine hydrochloride (Bentyl) has a direct relaxant effect on smooth muscle as well as antimuscarinic action. Dose is 20mg three times a day. This drug increases bladder capacity in patients with detrusor hyperreflexia.

Flavoxate hydrochloride (Urispas): direct inhibitory action on smooth muscle as well as anticholinergic and local analgesic (painkilling) properties. Recommended dose is 100-200mg three-four times daily. Results vary, with some reports of benefit in patients with unstable bladders, but no effect in trials in the elderly.

Theoretically, the drug should have the advantage of maintaining good bladder contractility during micturition, but the US guidelines (AHCPR) do not recommend its use.
Other drugs used have included: prostaglandin inhibitors, scopolamine and bromocriptine.

Stress incontinence:
Alpha adrenergic drugs: phenylpropanolamine hydrochloride is found in many prescription and over-the-counter (OTC) cold/cough preparations and antihistamines (anti-allergy). Typical dose is 25-75mg in sustained-release form, twice a day. It should not be used in patients with obstructive incontinence. Caution is necessary in patients with high blood pressure, overactive thyroid, and heart conditions.
Pseudoephedrine hydrochloride: 15-30mg three times a day
Hormonal replacement therapy (HRT) /Oestrogen: this helps to maintain and restore urethral tissue health in post-menopausal women.
Combined oestrogen/alpha-adrenergic agonist therapy: may be beneficial in post-menopausal women who have malfunction of the urethral sphincter muscles. Phenylpropanolamine (PPA: found in OTC preparations such as Dimetapp and Robitussin-CF) 25-100mg twice a day plus oestrogen tablets (dose varies). (Note: PPA is no longer available in US due to possibility of seizures)

Emptying dysfunction:
Parasympathetic nerve stimulation may be helpful in patients with an upper motor neurone neurogenic bladder, i.e. an under-active bladder that fails to empty properly.

Carbachol and bethanecol are choline esters that have been used to treat post-operative urinary retention. However, they have largely been superseded by the use of catheterisation.
Distigmine (Ubtetrid): inhibits the breakdown of the neurotransmitter acetylcholine (so works in the opposite way to anticholinergics): it may help patients with flaccid bladder. Dose is 5mg, half an hour before breakfast.

Dyssynergic bladder:
Alpha blockers: dybenzyline, Clonidine, Hytrin. Note that clonidine is sometimes used as an adjuvant analgesic (painkiller in conjunction with morphine or related drugs).

Obstructive urinary problems:
Alpha-blockers: useful for urge incontinence and in cases of prostate enlargement; they reduce the tone of smooth muscles in the urethra, decreasing urethral resistance and relieving symptoms of obstruction. Examples include: Doxazosin (Cardura), Terazosin (Hytrin), Tamsulosin (Flomax). Side-effects include: drowsiness, dizziness, postural hypotension (drop in blood pressure on standing up), depression, headache, dry mouth, nausea, rhinitis (runny nose), *urinary frequency and incontinence*, erectile disorders,

palpitations. They should not be used in patients with low blood pressure and micturition syncope (fainting when passing urine).

Chuang et al. ([770]) investigated the use of Botulinum toxin (BTX) in treating lower urinary tract dysfunction, reviewing medical literature on the topic. They found that injection of BTX is effective in the treatment of detrusor-sphincter dyssynergia, non-neurogenic pelvic floor spasticity, and refractory overactive bladder. Urodynamic assessment after sphincter injection with BTX showed reduced bladder voiding pressure, urethral pressure profile, and post-void residual urine. A similar decrease in bladder voiding pressure was seen after bladder injection, with an increase of the functional bladder capacity. Clinical improvement lasted for 3 to 14 months without significant adverse effects.
As a further benefit, BTX-A treatment inhibits afferent-nerve-mediated bladder contraction. This has an analgesic effect which may be useful in genitourinary tract pain syndrome, such as interstitial cystitis and prostatodynia.

Sexual function:

Two recent studies in Illinois, by Sand et al., presented at the annual scientific meeting of the American Urogynecologic Society (AUGS) in October 2002, found that women with overactive bladder who were treated with extended-release Ditropan (Oxybutinin) reported substantial improvement in sexual functioning including orgasm. In particular, this involved a reduction in the negative impact of bladder problems on the ability to enjoy sexual activity. The first study was a 12-week, open-label study of 235 women with urge incontinence and other overactive bladder symptoms, who received an individual titrated dose of 5- 30 mg oxybutynin. They completed daily urinary diaries and the 32-question Urge Incontinence Impact Questionnaire (U-IIQ) at baseline and post treatment. In the second study which was of 12 months' duration using a similar treatment regime, 901 subjects completed the 10-question Individual Incontinence Impact Questionnaire, at baseline and after three months of treatment. Dr. Peter Sand, of Northwestern University Medical School, in Evanston, Illinois, reported that both studies showed that up to one fourth of women with overactive bladder reported that the condition often or always negatively affects their sexual activities with the impact being especially severe among women with more than 14 episodes of incontinence weekly and those under the age of 40.

General measures to assist bladder function:

1. Avoid caffeine (a diuretic, it promotes increased urine) in coffee, tea, cola and chocolate, carbonated beverages
2. Drink plenty of water
3. Cranberry juice may be helpful in some people to reduce infection risk. Avoid citrus fruit juices
4. Avoid constipation as a loaded bowel can worsen incontinence

5. Keep bladder pressure low, empty on a regular schedule
6. Use the Crede manoeuvre to completely empty the bladder (press downwards and inwards on the lower abdomen whilst urinating.): unless you have dyssynergic bladder (may cause urine reflux)

Surgical techniques include:

- Sacral nerve stimulation (SNS): for intractable urgency and urge incontinence, also urinary retention due to spasticity of pelvic floor muscles, sphincter dyssynergia.
- Surgical correction of stress incontinence, to provide a sling support for the pelvic floor.

Spasticity

Management of spasticity is complex and requires input from a multidisciplinary team.

Consideration should be given to:

1. Prevention of provocative factors: including pain, constipation, infection and poor postural management.
2. Physical therapy: to maintain muscle and soft tissue strength, improve body symmetry and facilitate functional activity following upper motor neurone damage.
3. Medical treatment: depending on whether the spasticity is general, focal or regional. Focal spasticity may respond to oral agents such as baclofen (see above), intramuscular Botox, intrathecal agents such as baclofen, or surgical intervention.

Use of Botox (see above) should be decided using selection criteria that answer the following questions:

1. Is the problem amenable to this treatment?
2. Is there a significant component of muscle overactivity?
3. Is this focal and which muscles are involved?
4. What is the aim of the treatment?
5. How will treatment improve the patient's situation?
6. Are there any contraindications?
7. How will outcomes be evaluated?

In chronic spasticity, the focus of management may well be on symptomatic improvement (e.g. pain relief, better functional capacity), prevention of complications (e.g. contractures, immobility osteoporosis) as well as easing the carer burden.

The primary aim of treatment is to maintain length in spastic muscles and allow normal positioning of the limbs in order to prevent secondary soft tissue change.

60% of patients with moderate to severe Multiple Sclerosis require specific spasticity treatment. ([771])

Snow et al. ([772]) and Hyman et al. ([773]) have performed controlled trials of Botox in spasticity in patients with MS. Barnes et al. ([774]) recently published a paper on Spasticity in MS. They found a 47% incidence of

spasticity within their study population of MS patients. The authors noted "Individuals with spasticity were found to have significantly higher levels of disability than those who had no spasticity or clinically insignificant spasticity." They recommend strategies such as:

- Attention to underlying exacerbating factors
- Physiotherapy for gait training, positioning and seating
- Use of oral medication such as baclofen (see above)
- Use of focal injection techniques e.g. botulinum
- Intrathecal baclofen in severe cases
- Surgical measures

In their study population, they found that baclofen was used in 23 people (34%), but in 9 cases, suboptimally. Dantrolene sodium was only used in 7 people (10%) of whom 3 required further treatment adjustment. Diazepam was only used in 4 people (6%). Tizanidine had only just been introduced onto the UK market at the time of the study (1998/9) so was not being used, although the authors commented that a number of cases that were unresponsive to baclofen (developed tolerance) may well have been good candidates for the use of tizanidine.

6% of the study was given regular botulinum toxin injections.

68% were receiving active and ongoing physiotherapy, and a further 25% might well have benefited from this had they been referred.

Barnes et al. concluded: "A significant proportion of the population seemed to be inadequately treated with regard to oral medication."

Botulinum toxin has also been used in children with cerebral palsy.

CRPS

Hooshmand, an expert in CRPS, is keen on the preventive measures:

1. Early diagnosis: thermography is most helpful; EMG and nerve conduction tests may be normal
2. Early aggressive physical therapy.
3. Avoidance of unnecessary use of braces, crutches etc. and immobilisation for soft tissue injury
4. Avoidance of the use of ice on affected area; it constricts blood vessels and is a factor in instigating, aggravating and perpetuating RSD.
5. "*Avoidance of alcohol in any amount*
6. *Avoidance of narcotics and benzodiazepines in any amount and at any stage, except for clonopin used for seizure disorder*"
7. "*Avoidance of unnecessary surgery such as cutting and suturing in the area of scars", "unnecessary surgery... for spinal pain" (of nerve root contusion origin or chronic); avoidance of "unnecessary operations such as amputation, sympathectomy and injections with steroids*". He also includes surgery for improperly diagnosed carpal tunnel syndrome.

(From: Chronic Pain: Reflex Sympathetic Dystrophy, Prevention and Management, CRC Press, Boca Raton, Florida. 1993 H. Hooshmand, M. D.)

Essentially, treatment of CRPS is broadly similar to that of arachnoiditis: pain relief is effected as best possible using a variety of medications, often the triad of opiates, antidepressants and anticonvulsant.

Therapy that might benefit the inflammatory problems

- Hot/cold compresses
- Joint supports
- A carefully planned exercise regime that is tailored to individual needs and can be adjusted as appropriate in response to 'flare ups'.
- Dietary measures including supplements
- Medication such as anti-inflammatory drugs (NSAIDs), which might include steroids (NOT SPINALLY INJECTED!) at times of major exacerbation.
- Physiotherapy techniques such as ultrasound which can reduce inflammation

Osteoporosis

Skelton and Dinan (1999) suggested the following exercises for **falls management**: (FaME: Falls management exercise programme)

- Co-ordination/reaction
- Functional floor and standing activities: to improve neuromuscular skill and confidence
- Postural and gait training
- Targeted strengthening and stretching exercises
- Kinaesthetic awareness
- T'ai Chi adapted moves: 3-D
- Correction of muscle asymmetry

Being active cuts the rate of risk of fracture by 50%, although bone density is only changed by 2% so there must be other factors involved.

Leg Swelling

Swelling in the lower part of the body, particularly the ankles and calves is a fairly common problem in arachnoiditis, as it is with people who have had a spinal cord injury. It is a result of loss of muscle movement in the legs assisting with venous pumping of the blood back up to the heart.
In people with impaired leg muscle control, the blood in the veins is not efficiently pumped up out of the legs, whilst the arteries continue to bring blood into the legs, thereby creating a build-up of fluid pressure within the veins. The veins start to bulge, which causes the valves in their walls to fail; fluid components of

the blood leak out into the adjacent tissues, making the fascia stretch and tear. Even if the muscle could compress the veins at this stage, the fascia would stretch, so there would be compression but not flow. A vicious circle is established, with vein function becoming steadily poorer, leading to more swelling and thus worse function etc. If the fluid leakage out of the veins carries with it a pigment (haemosiderin) the affected tissues are stained purple or dark brown.

It is vital to understand that water pills (diuretics) are of no use in this situation.

The problem is 3-fold:

1. Lack of muscle strength in the calf causes loss of compression
2. Loss of valve integrity
3. Loss of fascial integrity/ support

The current state-of-the-art treatment uses a series of wraps that have several functions when used simultaneously: the first layer pads the leg; the second layer supports the fascia and the third gently compresses the leg circumferentially to bring the valves closer together. The fourth provides additional support for the veins and is self-adherent in order to prevent the inner layers from unravelling.

Venous insufficiency ulcers:

These are open wounds that result from tissue damage as a consequence of a build-up of waste products in the leg. The venous congestion and incompetent valves are again the root cause for this problem. There may be a quite widespread inflammatory response of redness, warmth, swelling and tenderness in the calf. This problem may be misdiagnosed as 'cellulitis.' Dressing open wounds without tackling the underlying cause is likely to be ineffective at best, and if antibiotics are used, could potentially allow the growth of resistant bacteria.

It is important to be vigilant against any skin breakdown from shoes/socks rubbing against the swollen areas, or indeed, sharp edges on wheelchairs or beds as this raises the risk of skin infection (cellulitis) and ulcers. As it is common for people to have reduced sensation, there is a risk of being unaware of damage to the skin and subsequent problems. Always check for redness and sores on a daily basis.

NOTE: Leg swelling associated with sudden onset of shortness of breath or chest pain requires urgent medical attention, especially if one leg is warmer than the other or is red.

If both legs swell, the following tips may help:

- Perform range of movement exercises
- Elevate your legs to or above the level of your heart for 10-15 minutes at a time, 4 or 5 times a day

FOOT CARE

Patients with neuropathy can lose the ability to feel pain, heat, and cold and may therefore be unaware of minor cuts, scrapes, blisters, or pressure sores that can cause serious complications if left untreated. Neuropathy can also cause deformities such as Bunions, Hammer Toes, and Charcot Feet. Because of the potentially serious consequences of neuropathy, extra precautions must be taken to prevent foot-related injuries. It is important to: Check the feet every day for cuts, blisters, cracked skin, calluses, etc. A mirror can be used if it is difficult to see the bottom of the feet. Wash the feet every day, dry thoroughly and rub skin lotion in to keep the skin soft. Smooth corns and calluses gently. Keep toenails trimmed. Avoid walking barefoot and ensure appropriate footwear (cushioned well fitted shoes with a wide toe box; removable insoles and orthotics may be helpful). Keep the feet warm and dry. Avoid heat from hot water bottles etc. and it is inadvisable to soak the feet for too long in a spa bath. Promote improved blood flow by putting the feet up when sitting, avoiding crossing the legs, stop smoking, perform gentle foot exercises.

Autonomic dysreflexia:

Prevention:

- Keep catheter equipment clean and draining freely
- Empty bladder routinely
- Follow a regular bowel programme (try to keep stool soft)
- Check skin daily
- Wear loose-fitting clothing
- Check for painful stimuli
- Empty bladder and bowel before sexual activity and consider using medication
- Carry an Alert card

What to do during an attack:

- Sit up or raise the head of the bed IMMEDIATELY
- Look for the cause of the irritation: check bladder/bowel/skin
- Remove the cause
- Catheterise /check catheter for kinks/empty bag: note: empty bladder slowly to avoid spasms; is an infection present? Treat as advised by physician
- If there is stool in the rectum, apply numbing gel, wait 5 minutes and remove stool gently.
- Loosen tight clothing; remove any sharp objects in pockets or on seat; reduce irritation from cuts/burns etc. with cold cloth and medication; trim ingrowing toenails after first anaesthetising the area (treat infection if present)
- If AD occurs during sexual activity, check for pressure on testicles or penis; stop, sit up and rest

Treatment of Hydrocephalus: Ventriculoperitoneal (VP) shunt: CSF diversionary shunt; complications: infection uncommon; obstruction; (50% likelihood); 10% risk of Subdural haematoma (blood clot) (especially after a fall)

FIBROMYALGIA (FMS)

Medications effective in the treatment of FMS appear to work mainly through an effect on deep sleep *(Goldenberg 1986).* They should be started at the lowest possible dose and increased every few days to a week to maximum relief of daytime FMS symptoms without unacceptable side effects. These include: trazodone (50mg starting dose); cyclobenzaprine (10-60mg taken an hour before bedtime); alprazolam (0.5-4mg taken half to one hour before bedtime) and diphenhydramine (50-300mg half to one hour before bedtime); amitriptyline (10-150mg taken 2 hours before bedtime).

Treatment of problems such as insomnia and anxiety should be regarded as secondary to pain relief because pain is most likely to be the source of the problem. Use of hypnotics and anxiolytics is thus inappropriate if pain relief remains suboptimal.

Myofascial pain syndrome

Approaches need to be holistic.

Consideration of the following points must be taken:

- Treatment of any underlying condition (pain management especially)
- Elimination of any aetiologies such as facet syndrome
- Stress reduction, sleep hygiene and psychological therapies to assist overall wellbeing
- Promotion of good posture and pain free active range of movement; attention to breathing etc.
- Use of massage, acupuncture, physiotherapy, exercise, etc. to interrupt the pain cycle and promote strengthening, conditioning and ergonomics to prevent re-injury.

RESEARCH

There are a number of different research facilities investigating various aspects of scarring, and therapeutic agents to prevent or reduce scar tissue.

For instance, rat studies have looked at axon regeneration in CNS damage, which can be prevented by scar formation. A resorbable polymer, Seprafilm has been piloted as a barrier to extrinsic scar formation and axon regeneration was improved. Reports on CNS regeneration suggest that chondroitinase may play a role in reducing scar formation in the CNS and the PNS (peripheral nervous system). ([775])

FibroGen is an American company that developed a product based on prolyl hydroxylase inhibitors. In 1998, the company reported on studies in which they "demonstrated a reduction in scar deposition with treatment

and little or no recurrence of scarring after treatment was stopped. In addition, increased apoptosis of the collagen-producing fibroblasts was observed in treated animals, which may explain why scarring did not recur after treatment ended." They claimed that their product would be useful in all types of abnormal scarring, including, "scarring after major surgeries such as laminectomies and discectomies."

In 1999, Llado et al. performed a dog study ([776]) to assess the use of expanded polytetrafluoroethylene (ePTFE) as a barrier to postoperative invasion of fibrous tissue into the laminectomy defect. They looked at laminectomised dogs 12 weeks postoperatively. They reported: "We conclude that the ePTFE spinal membrane, when properly implanted, is an effective barrier to postsurgical fibrous invasion of the vertebral canal. Clinical studies of use of this material in spinal surgery are warranted."

In Israel in October 2002 ([777]), there was a report on Tempostatin™, which has been found to delay scar tissue formation by its effects on stroma cells that produce collagen.
"Tempostatin™ is actually the `circuit breaker' of the scar formation process," according to Dr. Bruce Bach, CEO of the U.S.-Israeli biotechnology company Collgard, which is currently developing the substance. Its method of activity is somewhat paradoxical, because it actually slows down the healing process.
The agent has already been tested for safety in patient populations and deemed acceptable for use in controlled clinical trials (currently underway in Europe), although its effectiveness has so far been proved only in animals.

Italian authors Bocchi et al. looked in 1995 ([778]) at the various factors in pathological scar formation in burns. They outlined the treatment options available at that time, and suggested, "Corticosteroids are the most successful agents in the non-surgical therapy of burn scars. A few mechanisms of their action are known: they decrease collagen synthesis, inhibit fibroblast migration into the wound, and affect the inflammatory and local immune response." They included zinc oxide, hyaluronidase, retinoic acid and colchicines in their list of agents used to treat this type of problem. Hyaluronidase and colchicine have both been attempted in arachnoiditis, but there is no available data on the longer-term outcome.
Interestingly, the authors noted that vitamin E and zinc might be important factors: "Vitamin E is a membrane stabilizer which inhibits the liberation of lysosomal contents, having an anti-inflammatory effect which decreases tissue repair. Zinc seems to inhibit fibroblast action, although there are reports of a stimulation of collagen synthesis."
Also in 1995, Hinton et al. ([779]) looked at the use of intraoperative steroid, (slow release) in animals and found that "Dexamethasone acetate (Decadron...) significantly reduced the density of the scar tissue undermining the laminas. Steroids embedded in polymer did not change the scar formation in the back, but did decrease protein and DNA values in wound chamber tissues. CONCLUSIONS. Long-term release of small amounts of steroid from the polymer poly-carboxy-phenoxypropane does not appear to reduce scar at laminectomy sites but does decrease the protein: DNA ratio in wound chambers. In contrast, Decadron does not significantly alter the biochemistry of wound chamber tissue but does reduce scar in the back." However, the study only looked at the results 4 weeks after the laminectomy, so longer-term effects have yet to be evaluated.

A further study in 1995, by He et al. ([780]) used a rat model, and found that non-steroidal anti-inflammatory agents might offer a way of reducing post-operative scarring.

In 1999, Gerszten et al. ([781]) looked at rats 30 days after laminectomy to assess extent, density, and arachnoidal involvement by fibrosis. They reported: "Low-dose external beam radiation therapy administered before or after laminectomy in a rat model significantly decreases the extent, density, and arachnoidal involvement of peridural fibrosis. This technique may improve the outcome of patients who undergo reoperations for recurrent radicular and/or low back pain after successful lumbar discectomy in whom there is a significant amount of peridural fibrosis."

More recently a Turkish team ([782]) looked at an animal model for the use of external radiation in comparison with the use of a spinal membrane (as described above under treatment). They found: "This preliminary study showed that high-single-fraction/low-total-dose administered postoperatively can successfully inhibit postsurgical epidural fibrosis as effectively as applied spinal membrane."

In 2002, French authors Lui et al. ([783]) published the results of a rat study looking at the use of a collagen-based sealant, Gel Amidon Oxyde (GAO), in preventing the reformation of epidural scar adhesions in an adult rat model of laminectomy. They stated: "The authors found that GAO may be a safe and effective antiscarring adhesion biomaterial in vivo. When placed into the laminectomy site, GAO may prove beneficial in preventing the formation and reformation of epidural scar adhesions in humans."

This year, Lee et al. ([784]), in Germany, reported on the use of TachoComb®, an agent they compared with Spongostan®, and Tabotamp®. They found that in rats undergoing laminectomy, TachoComb reduced the amount of epidural fibrosis considerably, although the authors noted: "However, complete prevention of scar tissue formation was not achieved."

In Manchester, Professor MWJ Ferguson (at the School of Biological Sciences) has been studying adult wound healing in relation to that in the embryo. There is known to be a substantial difference between them, mostly by virtue of the fact that the immune system in the embryo is still developing. His team reduced the levels of growth factors present at high levels in the adult, but low levels in the embryo, e.g. Transforming Growth Factor Beta 1 and Beta 2 (TGFb1 and TGFb2) or elevated levels of growth factors present at high levels in an embryonic wound, but low levels in the adult wound (TGFb3). They reported in the prestigious journal *Nature* in 2002 ([785]): "These experimental manipulations resulted in adult wounds that healed perfectly with no signs of scar formation." It has been known for some time that transforming growth factors may have potential in minimising scar tissue formation. Choi et al. ([786]), in 1996, found that in animals, "antisense TGF-beta 1 ODN could be used for ameliorating scar formation during wound healing."

The Children's Hospital in Boston, Massachusetts, has been investigating the use of topical mitomycin C, an antibiotic currently in use in chemotherapy ([787]). It is known to reduce collagen formation in vitro and has been used for some time in eye surgery ([788],[789]), as well as otorhinolaryngology (ear, nose and throat) ([790]) and Chung et al. ([791]) found that it "may reduce the incidence of postoperative adhesions" after sinus surgery. The agent is applied to tissue prone to scarring, for 2-4 minutes at the end of an operation. There are no published results from this study as yet, although a study has just been reported on the use of

topical mitomycin in the prevention of scar tissue formation in the postsurgical external auditory canal, which failed to demonstrate any efficacy ([792]).

Mitomycin is an antimetabolite chemotherapy agent and as such carries a risk of severe adverse effects and is likely therefore be unsuitable for use in the subarachnoid space. However, there is another potential treatment for use in eye surgery to reduce the incidence of scarring, amniotic membrane transplantation, which seems to perhaps be a little less effective than mitomycin C, but carries much less risk of the adverse effects. This treatment is still at clinical trials stage. ([793])

We can see that over the past 15 years or so, a number of studies have been performed in an attempt to prevent scar formation. No doubt there are other initiatives underway to find treatment options for scars in all parts of the body. I shall be attempting to keep abreast of any important developments.

As regards removal of established scar tissue, as we have seen (See Treatment), the problem of recurrence is the main stumbling block; therefore this is a vital area for research.

CONCLUSIONS:

Aldrete recently noted in his online Newsletter (December 2002), that doctors who have already been investigating spinal cord injuries are carrying out research in Mexico City. Rat studies have been used to develop an experimental model of arachnoiditis. Dr. Aldrete notes that this will be vital in permitting the comparison of effects from chemicals such as saline, polyethylene glycol etc. with those produced by phenol. He also remarked that surgery alone could cause meningeal damage, nerve root clumping and axon demyelinisation.

Aldrete comments in his book, "Arachnoiditis -The Silent Epidemic": "The tremendous impact that this disease has among middle-aged, productive people is enormous.... with most of them disabled, divorced, depressed, angry, involved in litigation," and in his commentary at the end of the chapter, concludes that:

"Since the most common cause of lumbar ARC is usually an iatrogenic event resulting from a complication of a diagnostic or therapeutic procedure, the medical community must therefore take an introspective look at itself without skepticism and reluctance. There is little doubt that today, interventional procedures of the spine are the etiology in most of these cases."

Dr. Bourne, whose wife suffered from arachnoiditis, wrote: ([794]): "The relentless and progressive pain syndrome of arachnoiditis is taxing to the patient's morale. In many instances doctors, relatives and friends fail to realise that the pain can be as bad as terminal cancer, without the prospect of death to end the suffering. Well-meaning enquiries as to whether there is any improvement with the implication that there must inevitably be improvement...are distressing to the patient.

There are sympathetic doctors, relatives and friends who expect the patient to be brave, stoical and cheerful. In the end the patient yearns for less exhortation and more compassion. Compassion is an important consequence of comprehension of the existence and nature of arachnoiditis."

We must keep in mind that, far from being a medical anachronism, adhesive arachnoiditis continues to present an ongoing challenge to the medical community and remains a source of terrible suffering throughout the world.
The profile of this condition needs to be raised in order to initiate vital research into possible avenues of treatment and better still, prevention.

The 2001 New Zealand report's closing recommendation serves as a timely reminder:

"Prevention will be an important aspect of health strategies to address this condition given the recognised etiology...particularly the prevention of post-operative and post-injection complications."

Numerous support groups around the world strive against great odds (often run by sufferers) to bring the story of arachnoiditis into both the medical and public arenas. Many individuals struggle day to day to maintain hope in the face of an incurable and devastating condition. They remain faceless and nameless, but their courage should not be forgotten.

The NZHTA report, whilst commending the involvement of various support groups, citing them as a useful resource and "an important impetus to future research", acknowledged, "It is not clear how co-ordinated and systematic research into arachnoiditis will proceed."
Nevertheless, we must continue to work steadily and determinedly towards what may thus far seem an invisible and maybe impossible goal.

In summary, we need a 3-pronged attack on arachnoiditis:

1. **Recognition of cases, leading to statistics on prevalence.**
2. **Proactive approach to treatment**
3. **Prevention of further preventable cases.**

In order to achieve these aims we need:

Education and Research

As Dr. Charles Burton wrote in 1999,

"The subject of adhesive arachnoiditis is still something no one really seems to hear anything about. They will, I assure you, continue to hear about it because it is still a clear and present health affliction and we will do our best to continue to make the public aware of this condition and hopefully, to bring some recognition and respect to sufferers."

I hope this book will help raise awareness, provide education and promote research. Most of all, I hope that it gives sufferers hope for the future, whilst aiding them in the midst of their present afflictions.

Dr. Sarah A. Andreae-Jones (Smith) MB BS
Patron of the Arachnoiditis Support Group, Knowsley,
ASAMS, New Zealand and COFWA, USA.

GLOSSARY:

Adhesions: A fibrous band or structure by which parts abnormally adhere.

Aetiology: study of disease causes

Allodynia: ordinarily nonpainful stimuli evoke pain.

Anaesthesia: The loss of feeling or sensation

Analgesia: of insensitivity to pain, even though the subject is fully conscious.

Analgesia dolorosa: (also analgesia algera or anaesthesia dolorosa): Spontaneous pain in a body area that lacks sensation.

Analgesic: an agent that brings about analgesia

Arachnoid: lies within the vertebral canal and surrounds the spinal cord and the vertebral portion of the subarachnoid space. It extends from the foramen magnum to the S-2 vertebral level. Since the spinal cord ends at the L-2 vertebral level, a wide separation occurs between the arachnoid and pia mater, the lumbar cistern, filled with cerebrospinal fluid in which the cauda equina is suspended.

Arachnoid cyst: A fluid-filled cyst lined with arachnoid membrane, frequently situated near the lateral aspect of the fissure of Sylvius; usually congenital in origin. Synonym: leptomeningeal cyst.

Arnold Chiari malformation: Chiari I herniation of medulla and cerebellar tonsils, 4th ventricle in normal position, Chiari II herniation of medulla, tonsils, vermis, 4th ventricle at foramen magnum, myelomeningocele, aqueductal stenosis most likely to be hydrocephalus, Chiari III further herniation, 4th ventricle below foramen magnum, encephalocele or myelomeningocele associated with: agenesis of corpus callosum, syrinx

Arteriovenous malformation: A tangled collection of abnormal blood vessels where there is an abnormal communication between the arterial and venous systems, mostly congenital. Common sites include; skin,

liver, brain, brainstem and spinal cord, where they may cause headaches, seizures or bleeding (subarachnoid haemorrhage). Synonym: haemangioma

Aseptic meningitis: A meningeal reaction in the cerebrospinal fluid sometimes occurring in the absence of an infecting organism. It can be due to a virus, foreign substance, diagnostic or therapeutic procedure, or to a tumour

Asymptomatic: Without obvious symptoms of disease.

Atrophy: A wasting away, a diminution in the size of a cell, tissue, organ or part.

Autoimmune: A condition in which an individual's immune system starts reacting against his or her own tissues, causing diseases such as lupus.

Autonomic nervous system: not under conscious control, comprising two antagonistic components, the sympathetic and parasympathetic nervous systems.

Regulates key functions including the activity of the cardiac (heart) muscle, smooth muscles (e.g., of the gut), and glands. The autonomic nervous system has two divisions: 1. Sympathetic nervous system: accelerates the heart rate, constricts blood vessels, and raises blood pressure. 2. Parasympathetic nervous system slows the heart rate, increases intestinal and gland activity, and relaxes sphincter muscles.

Baricity: The weight of one substance compared to the weight of an equal volume of another substance at the same temperature.

Calcification: The process by which organic tissue becomes hardened by a deposit of calcium salts within its substance.

Calcify: To deposit or lay down calcium salts, as in the formation of bone.

Carpal tunnel syndrome: disturbance of median nerve function in the wrist as the nerve passes through the carpal tunnel.

Cauda Equina: A bundle of spinal nerve roots which arise from the termination of the spinal cord proper, it comprises the roots of all the spinal nerves below L1.

Cauda Equina Syndrome: A clinical syndrome characterised by dull pain in the lower back and upper buttock region, analgesia in the buttocks, genitalia (or thigh), accompanied by a disturbance of bowel and bladder function.

Central nervous system: brain, cranial nerves and spinal cord. It does not include muscles or peripheral nerves.

Acronym: CNS

Central nervous system depressants: A very loosely defined group of drugs that tend to reduce the activity of the central nervous system. The major groups included here are ethyl alcohol, anaesthetics, hypnotics and sedatives, narcotics, and tranquillising agents (antipsychotics and antianxiety agents).

Clinical syndrome: represents a typical constellation of physical (and laboratory) findings that may be seen as part of a primary disease process.

Clinical trial: Research study conducted with patients, usually to evaluate a new treatment or drug.

Cerebrospinal axis: The central nervous system; the brain and spinal cord.

Cerebrospinal fluid: A clear, colourless fluid that fills the ventricles of the brain and the central canal of the spinal cord.

Cerebral ventricles: fluid-filled spaces in the brain

Cervical: Pertaining to the neck or to the neck of any organ or structure.

Chemolysis: The dissolving of the nucleus pulposus of a displaced intervertebral disk, usually by the direct injection of a proteolytic enzyme, especially chymopapain, into the diseased disk.

Chiari: see Arnold Chiari malformation

Collagen: The protein substance of the white fibres (collagenous fibres) of skin, tendon, bone, cartilage and all other connective tissue. Collagenous= pertaining to collagen, forming or producing collagen.

Commensal: living within the body, as part of the normal flora.

Connective tissue: less specialised tissue that is rich in extracellular matrix (collagen, proteoglycan etc.) and that surrounds other more highly ordered tissues and organs.

Contiguous: Adjacent or in actual contact.

Dermatome: (adj. Dermatomal) the area of the skin supplied by a spinal nerve.

Diabetic neuropathy: Long standing or poorly controlled diabetes can cause permanent peripheral and autonomic nerve dysfunction known as diabetic neuropathy.

Diaphoresis: Perspiration, especially profuse perspiration. Synonym: sudoresis.

Discectomy: Excision, in part or whole, of an intervertebral disk. Synonym: discotomy.

Discitis: Inflammation of an intervertebral disk or disk space which may lead to disk erosion. **Discogram:** an investigation imaging the intervertebral disc by injection of dye and X-ray.

Dura: dura mater.

Dural sac: = thecal sac; contains the three meningeal layers

Dural tear: a frequent, usually inconsequential, complication of lumbar laminectomy, occurring in perhaps as many as 1 in 20 lumbar stenosis decompression operations. Only a very small number of these require intervention.

Dysaesthesia: An unpleasant abnormal sensation, whether spontaneous or evoked.

Dystonia: Disordered tonicity of muscle.

Encapsulated: wholly confined to a specific area, surrounded by a capsule. Localised.

Encephalopathy: Any degenerative disease of the brain.

Endoneural: Having to do with a nerve.

Epidural: within the spinal canal, on or outside the dura mater; synonyms extradural and peridural.

Epidural fibrosis: scar tissue in the space outside the dural sac; synonyms: peridural; extradural

Failed Back Surgery Syndrome: synonym: Post laminectomy syndrome; recurrent back/leg pain after surgery.

Fascia: The flat layers of fibrous tissue that separate different layers of tissue.

Fibrin: The insoluble protein formed from fibrinogen by the proteolytic action of thrombin during normal clotting of blood; forms the essential portion of the blood clot.

Fibrinolytic: causing the dissolution of fibrin by enzymatic action

Fibrosis: The formation of fibrous tissue, fibroid or fibrous degeneration the term usually refers to tissue laid down at a wound site well vascularised at first (granulation tissue) but later avascular and dominated by collagen rich extracellular matrix, forming a scar.

Foramen (pl. foramina): A small opening, perforation, or orifice; a fenestra.

Granuloma: Chronic inflammatory lesion characterised by large numbers of cells of various types (macrophages, lymphocytes, fibroblasts, giant cells), some degrading and some repairing the tissues.

Hemiparesis: weakness on one side of the body

Herniation: Bulging of tissue through an opening in a membrane, muscle or bone.

Hydrocephalus: dilatation of the cerebral ventricles, most often occurring secondarily to obstruction of the cerebrospinal fluid pathways and accompanied by an accumulation of cerebrospinal fluid within the skull, the fluid is usually under increased pressure, but occasionally may be normal or nearly so.

Hyperaesthesia: A neurologic symptom where there is an unusual increased or altered sensitivity to sensory stimuli.

Hyperbaric: Characterised by greater than normal pressure or weight, applied to gases under greater than atmospheric pressure, as hyperbaric oxygen or to a solution of greater specific gravity than another taken as a standard of reference.

Hyperthyroidism: excessive thyroid activity causing increased metabolic rate, enlargement of the thyroid gland, rapid heart rate, high blood pressure and various secondary symptoms.

Hypothyroidism: A deficiency of thyroid activity.

Iatrogenic: Induced inadvertently by the medical treatment or procedures or activity of a physician. synonym: nosocomial

Idiopathic: unknown cause

Inflammation: A localised protective response elicited by injury or destruction of tissues, which serves to destroy, dilute or wall off (sequester) both the injurious agent and the injured tissue.
It is characterised in the acute form by the classical signs of pain (dolor), heat (calor), redness (rubor), swelling (tumour) and loss of function (functio laesa).

Intervertebral: Situated between two contiguous vertebrae.

Intervertebral disc: The intervertebral discs or nucleus pulposus are fibro-cartilaginous and lie between the vertebral bodies in the spine.

Intracranial pressure: The pressure the cerebrospinal fluid exerts on the brain.

Laminectomy: surgical procedure including removal of a portion of the bone comprising a vertebra.

Leptomeninges: The two delicate layers of the meninges, the arachnoid mater and pia mater (vs. The tough pachymeninx or dura mater), considered together; by this concept, the arachnoid and pia are two parts of a single layer, much like the parietal and visceral layers of a serous membrane or bursa; although separated by the subarachnoid space they are connected via the arachnoid trabeculae and become continuous where the nerves and filum terminale exit the subarachnoid space (the cerebrospinal fluid-filled space bounded by the leptomeninges).

Localised: A disease found only in the original site, with no spread to other organs.

Loculation: A loculate region in an organ or tissue, or a loculate structure

Lumbar: Pertaining to the loins, the part of the back between the thorax and the pelvis.

Lymphatic system: The tissues and organs (including the bone marrow, spleen, thymus and lymph nodes) that produce and store cells that fight infection and the network of vessels that carry lymph. Lymph is an almost colourless fluid that bathes body tissues and is found in the lymphatic vessels

Meninges: The surrounding membranes the brain and spinal cord. There are three layers: the dura mater (outer), arachnoid membrane (middle) and the pia mater (inner layer).

Meningism: The symptoms and signs of meningeal irritation

Meningitis: Inflammation of the meninges.

Mononeuropathy: Disorder involving a single nerve.

Mononeuropathy multiplex: inflammation of several nerves usually in unrelated portions of the body.

Myelogram: diagnostic procedure where radiopaque contrast dye is injected into the spinal canal.

Myoclonus: Twitching or spasm of a muscle or a group of muscles.

Myelomalacia: Softening of the spinal cord.

Myelopathy Any disease affecting the spinal cord.

Myopathy: Any disease of a muscle.

Narcotics: Originally, agents that caused somnolence or induced sleep; now, any derivative, natural or synthetic, of opium or morphine or any substance that has their effects.

Neurogenic: Arising from or caused by the nervous system.

Neuroimmunomodulation: a complex interaction between the nervous system and the immune system.

Neuropathic: functional disturbances and/or pathological changes in the peripheral nervous system.

Neurotransmitter: Any of a group of substances that are released on excitation from the axon terminal of a presynaptic neuron of the central or peripheral nervous system and travel across the synaptic cleft to either excite or inhibit the target cell. E.g. acetylcholine, noradrenaline, adrenaline, dopamine, glycine, y aminobutyrate, glutamic acid, substance P, enkephalins, endorphins and serotonin.

Oedema: abnormally large amounts of fluid in the intercellular tissue spaces of the body, may be localised, due to venous or lymphatic obstruction or to increased vascular permeability or it may be systemic due to heart failure or renal disease.

Collections of oedema fluid are designated according to the site, for example ascites (peritoneal cavity), hydrothorax (pleural cavity) and hydropericardium (pericardial sac). Massive generalised oedema is called anasarca.

Optochiasmic: in the region of the optic chiasm, the crossover point of the two optic nerves from the back of the eyes.

Osteoporosis: A reduction in the amount of bone mass, leading to fractures after minimal trauma.

Pachymeningitis: Inflammation of the dura mater or outer membrane of the brain.

Paraesthesia: an abnormal sensation, as burning, prickling, formication, etc.

Paresis: weakness (cf. Paralysis= total loss of power)

Paraparesis: weakness in the lower part of the body

Percutaneous: Performed through the skin, as injection of radiopaque material in radiological examination or the removal of tissue for biopsy accomplished by a needle.

Perineural: surrounding a nerve

Peripheral nerves: The nerves outside of the brain and spinal cord, including the autonomic, cranial, and spinal nerves.

Pia: The delicate and highly vascular membrane immediately investing the brain and spinal cord.

Polyneuropathy: A disease process involving a number of peripheral nerves.

Prolapse: The falling down or sinking, of a part or viscus, procidentia.

Prolapsed disc: abnormal protrusion (bulging), herniation or prolapse of a vertebral disc from its normal position in the vertebral column. The displaced disc may exert force on a nearby nerve root

Prognosis: forecast of the probable outcome of an attack or disease

Pseudomeningocele: an extension of the subarachnoid space into the soft tissue surrounding the central nervous system. Unlike meningocele, pseudomeningocele is cerebrospinal fluid not bounded or confined by a biological membrane.

Radiculopathy: the radicular nerve (nerve root) is compressed by the prolapsed disk is referred to as a radiculopathy. This problem tends to occur most commonly in the cervical and lumbar spine.

Raynaud's Phenomenon: a condition causing abnormal response to cold in the extremities causing pallor, pins and needles and pain, followed by redness.

Regional anaesthesia: Use of local anaesthetic solution(s) to produce circumscribed areas of loss of sensation; a generic term including conduction, nerve block, spinal, epidural, field block, infiltration, and topical anaesthesia.

Rheumatology: branch of medicine dealing with arthritis and related conditions

Rhinosinusogenic: originating from chronic infection in the nose/nasal sinuses

Sacral: Of or pertaining to the sacrum; in the region of the sacrum.

Sacrum: The triangular-shaped bone lying between the 5th lumbar vertebra and the coccyx (tailbone). It consists of 5 vertebrae fused together and it articulates on each side with the bones of the pelvis (ilium), forming the sacroiliac joints.

Saddle anaesthesia: loss of sensation in buttocks, perineum, and inner surfaces of the thighs.

Stenosis: Narrowing or stricture of a duct or canal. Spinal stenosis: An abnormal narrowing of the spinal canal or lateral foramina (through which nerve roots runs) that may be either congenital or acquired.

Subarachnoid haemorrhage: bleeding into the subarachnoid space; often due to a ruptured cranial aneurysm

Subarachnoid space: space between the arachnoid and pia mater, traversed by delicate fibrous trabeculae and filled with cerebrospinal fluid. Large blood vessels supplying the brain and spinal cord lie in the subarachnoid space.

Syringomyelia Syrinx, congenital: 90% associated with Arnold-Chiari; **acquired**: trauma, tumour, infection, haemorrhage, etc.

Sudomotor: autonomic (sympathetic) nerves that stimulate the sweat glands to activity.

Symptoms: manifestations of disease and pathological conditions which may occur in various diseases and different organs

Systemic Lupus Erythematosus: an autoimmune condition causing a wide variety of symptoms throughout the body and often associated with a butterfly-shape facial rash. More common in women.

Sweet's syndrome: rare condition characterised by red-brown plaques and nodules, frequently painful occurring primarily on the head, neck and upper extremities.

The patients will also have fever and increased white blood cell counts (neutrophils). In approximately 10% of the patients there is an associated malignancy, most commonly acute nonlymphocytic leukaemia. The idiopathic form (unknown cause) of Sweet's syndrome is seen more often in females following a respiratory tract infection.

Tarlov's cyst: A perineural cyst found in nerve roots of the lower spinal cord

Tinnitus: ringing, buzzing, roaring, clicking, etc. in the ears.

Theca: A sheath; a case, a capsule; thecal sac= dural sac

Thoracic: Pertaining to or affecting the chest. (thorax)

Tonicity: normal tension of tissues; in muscle, it is active resistance to stretch

Vertigo: An illusion of movement, a sensation as if the external world were revolving around the patient (objective vertigo) or as if he himself were revolving in space (subjective vertigo).

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