

# *Australasian Musculoskeletal Medicine*



- Musculoskeletal medicine in Australia
- CT-guided ozone nucleolysis
- An evidence-based approach to human dermatomes
- Joint hypermobility and motor control
- How effective is glucosamine in osteoarthritis
- The endocannabinoid system

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# Editorial:

## Is it time to consign the term “nonspecific low back pain” to history?

**Dr Thomas Baster, Newnham Rd Medical Centre, Wishart, Australia. Email: drtombaster@gmail.com**

Welcome to the 2013 edition of *Australasian Musculoskeletal Medicine* journal. There is much of interest in this edition and I thank the authors of each article for their contribution. Specifically I would like to mention Dr Kyal Agraval and Ella McGrath for their contributions. Both were sponsored by the AAMM to attend the Wellington conference and it is gratifying to receive excellent articles on musculoskeletal topics from these young colleagues. Kyal is now a resident in a busy Melbourne hospital and many of us remember the long tiring hours involved in such work. She is to be commended for finding the time in writing the article on the discovery of the cause of radicular pain. Similarly, Ella McGrath, with a review of the best evidence regarding glucosamine for osteoarthritis, has written a scholarly article with a conclusion that provides useful clinical advice.

In the November 2012 edition of *Medicine Today*<sup>1</sup> an article was published titled “Nonspecific low back pain—Manage initially with reassurance, activity and analgesia”.<sup>1</sup> Whilst much of the article contained useful and valid information, the recommendations for the management of persistent pain were contrary to what some members of the Association would consider appropriate, especially in regards to radiofrequency denervation and spinal injections, with the statement that such are not supported by the “evidence”. The article stimulated considerable online discussion and Dr Geoff Harding, Dr Scott Masters and myself submitted alternative viewpoints to *Medicine Today* that unfortunately have not been published.

The article mentioned above is not the only one in the medical literature to use the term “nonspecific low back pain” and it implies that it is not possible, necessary, or useful to elucidate an underlying anatomical diagnosis once “red flag” conditions have been excluded. One wonders if the use of this label is akin to accepting “chest pain” without further differentiation or “abdominal pain” as a diagnosis and most

competent medical practitioners would not readily accept such. Should the term “nonspecific low back pain” also not be accepted and should it be consigned to the history books as a quaint description used in the absence of the understanding of the underlying pathology?

There are now multiple published reports<sup>2-5</sup> where patients with chronic spinal pain have been extensively investigated to determine the underlying structures responsible for their symptoms. This has involved the use of local anaesthetics of different duration of action (usually lignocaine and bupivacaine) injected into suspected pain-generating structures and recording patient pain responses. The duration of pain relief should correlate with the known duration of effect of the anaesthetic agent used. By using different types of local anaesthetics, with precise placement using imaging at certain spinal anatomical structures, it is possible to derive some useful general clinical information.

Such information includes:

1. The anatomical structures that can cause chronic lumbar spinal pain
2. The prevalence figures for each structure identified above
3. Correlation with the patient symptoms and clinical examination
4. Correlation with “standard” investigations – x-rays, CT or MRI.

However, such information would be only of academic interest if patient outcomes, in terms of reduced pain and disability, are not improved. Thus further considerations are required:

5. Are there effective and readily available treatments for structural causes of chronic low back pain?
6. Does treatment result in improved patient outcomes compared to the “nonspecific” approach?

There have been a multitude of structures proposed as causing back pain. However, to be plausible and clinically useful certain criteria need to be considered.

- The supposed structure should be innervated and appropriate

stimulation causes pain in normal volunteers.

- Proposed structures should be susceptible to diseases and injuries that are known to be painful, similar to other anatomical sites in the body.
- A diagnostic test is available, of known validity and reliability, for determining the structure causing the patient’s pain.

In detail the structures postulated as a possible cause of chronic low back pain are outlined in the table on the next page (adapted from *Clinical Anatomy of the Lumbar Spine and Sacrum*, 4th ed., by Nikolai Bogduk, Elsevier).

Other studies that have specifically focussed on lumbar discs, ZAJ and SIJ include those in the second table on the next page.

Considering these tables with the plethora of “unknowns” and the wide variation in the figures of the second table, what “coal face” conclusions can reasonably be made? In broad terms it seems that discogenic pain occurs in about 40% of cases. Similarly ZAJ about 25% and SIJ about 25%. A more detailed consideration of these and other studies, however, indicates that in older patients the figures for ZAJ pain are probably higher – about 40% and in younger patients the discogenic cause is more likely to be around 60%. These figures are worth considering as an initial basis of differentiating an individual clinical case. Using simple arithmetic on the above averages leaves only about nine cases in 100 unexplained – that is, not of discogenic, zygoapophysial or sacroiliac joint aetiology. This is quite a low figure.

The next relevant issue is whether the clinician can determine the underlying pathological subtype clinically without recourse to expensive investigations. Unfortunately it does not seem to be the case with any degree of certainty. There are many studies demonstrating that we are largely unable to definitely diagnose an underlying aetiology. This is similar, however, to other areas of medicine where

Structure or cause	Innervated	Pain in normal volunteers	Pathology known	Identified in patients	Prevalence in chronic back pain
Vertebral bodies	Yes	No	Yes	Yes	Rare
Kissing spines	Yes	No	Presumed	Yes	Unknown
Lamina inapaction	Yes	No	Presumed	Yes	Unknown
Spondylolysis	Yes	No	Yes	Yes	<6%
Muscle sprain	Yes	Yes	Anecdotal	Unknown	Unknown
Muscle spasm	Yes	Yes	No	Unknown	Unknown
Muscle imbalance	Yes	No	No	Uncontrolled	Unknown
Trigger points	Yes	Yes	No	Unreliable	Unknown
Iliac crest syndrome	Yes	Yes	No	Yes	30-50%
Compartment syndrome	Yes	No	No	Yes	Unknown
Fat herniation	Yes	No	Yes	Yes	Unknown
Dural pain	Yes	Yes	Presumed	Yes	Unknown
Epidural plexus	Yes	No	No	Yes	Unknown
Interspinous ligament	Yes	Yes	Presumed	Uncontrolled	<10%
Iliolumbar ligament	Probably	No	No	Controlled studies	Unknown
Sacroiliac joint pain	Yes	Yes	No	Controlled studies	13% ( $\pm 7\%$ )
Zygapophysial joint pain	Yes	Yes	No	Controlled studies	<10% (32% elderly)
Internal disc disruption	Yes	No	Yes	Controlled studies	39% ( $\pm 10\%$ )

a patient with chest pain might clinically be suspected having ischaemic problems but further investigation is required. Yet some factors in the history and examination of a case of chronic lumbar spinal pain do improve our odds of making the correct diagnosis. These include the Revel criteria<sup>16</sup> where age greater than 65, pain not increased by coughing, not worsened by hyperextension, not worsened by forward flexion and relieved by recumbency makes a diagnosis of ZAJ pain more likely. All the fancy bedside tests don't really add much apart from possibly impressing the patient.

In the exercise of attempting a specific diagnosis the next logical step, similar to a chest pain case (if the situation is reasonable, that is, severe chronic pain and disability) to investigate will require some type of imaging. Several studies have shown that degenerative discs and ZAJ are ubiquitous<sup>17</sup> and thus such findings are probably meaningless. However an MRI with findings of modic changes, a black disc in the clinical context of suspected discogenic pain is probably significant.<sup>18</sup> Similarly a positive spect scan report in the context of an older patient with possible ZAJ pain is also useful.<sup>19</sup> Whilst provocative discography is available to determine a discogenic case it is probably not a "coalface" investigation and is more relevant to patients being considered for surgery.

By this stage the patient has at least been given the courtesy of a diagnosis based on sound clinical reasoning and some imaging, even if further treatment is not undertaken.

Finally acknowledgement must be made

Authors	cLBP duration	Av Patient Age	# Patients	Disc	Results% ZAJ	SIJ
DePalma <sup>6</sup>	12 months	54.4 years	28	25	17.8	42.9
DePalma <sup>7</sup>	2 years	42.5 years	27	56	19	26
DePalma <sup>8</sup>			156	42	31	18
Maigne <sup>9</sup>	4.2 months	45.3 years				18.5
Manchikanti <sup>10</sup>	9.1 years	47.5 years	120	26	40	26
Schwarzer <sup>11</sup>	18.5 months	36.7 years	92	39		
Schwarzer <sup>12</sup>			43			30
Schwarzer <sup>13</sup>			92		8.7	
Schwarzer <sup>14</sup>	7 years	59 years	57		40	
Manchikanti <sup>15</sup>			438	39		
			<b>Average</b>	<b>38</b>	<b>26</b>	<b>27</b>

that treatment for chronic discogenic back pain is frustrating and is often ineffective. There is much effort being made into developing treatments for this condition. In this issue of the *Australasian Musculoskeletal Medicine* journal Dr G Koulouris reports on one such development – the use of ozone to denervate painful discs. At least hope can be given to our patients that we acknowledge their problem is real and that research is proceeding to provide a "cure" for them.

Yet the situation that applies to discogenic pain does not apply to the significant proportion of patients with ZAJ pain where medial branch blocks and radiofrequency denervation do provide significant symptom relief. SIJ pain is also temporarily relieved by intra-articular steroid and local anaesthetic injections.

In conclusion, the diagnosis of nonspecific low back pain is probably a "lazy" diagnosis

and should be used only in a broad sense when speaking generally of this clinical condition. It is reasonable I believe to use a term such as "lumbar spinal pain of unknown aetiology" until further assessment is undertaken, but overall I believe clinicians involved in the care of chronic lumbar pain patients should attempt to determine the underlying pathology if it is reasonable to do so.

On a separate note I look forward to meeting with many of you at the next combined AAMM/AFMM/NZAMM conference in the Blue Mountains in early October.

Details of this are provided elsewhere in this journal. The program provides a good mix of subjects that should appeal to those practising musculoskeletal medicine.

I trust you will enjoy reading the 2013 AMM journal.

- Tom Baster

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**AUSTRALIAN ASSOCIATION OF MUSCULOSKELETAL MEDICINE**  
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*What Works On The Front Line*

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# From the AAMM President

The AAMM will soon have a new website with a more up-to-date look, and be more user friendly than the previous one. It has been redesigned under the watchful eyes of Margi Taylor and Ramona Chryssidis, with some additional input from Tom Baster and myself. We owe Margi and Ramona a debt of thanks for their efforts – as we all know, the AAMM is a voluntary organisation, and things such as designing a new website depends heavily on the goodwill and time of the members, especially those on the committee.

When it is finally “live” the secretary will advise you, probably via the quarterly newsletter or by separate email. Make sure you take a look. It will be a work in progress and there are bound to be a few topics which will need tweaking. Please advise the secretary if there is something missing – especially addresses or pages that do not work properly.

The state of musculoskeletal medicine in Australia is such that anyone who wants to “specialise” in the discipline is disadvantaged by the fact that we are not seen as GPs and we are not recognised as specialists by AHPRA, the RACGP or by the other Colleges. This makes life difficult when it comes to earning a living because we have to charge fees which leave a considerable gap for the patient.

Those of us who practise full time in musculoskeletal medicine do not have access to the various alternative funding programs offered to “normal” GPs such as the PIP payments. Of course, if you are a doctor working in general practice and have an interest in musculoskeletal medicine, the situation is different – you are then able to participate in those blended payment schemes and still be considered to be a “real” GP by the RACGP.

So why take on full-time musculoskeletal medicine? From a personal perspective, when I commenced practising musculoskeletal medicine, it was as part of a general practice setting.

However, as time went by, more and more patients were coming to see me purely for musculoskeletal consultations. This meant that I had to make a choice, either continue with part-time musculoskeletal medicine and part-time general practice, or make a decision and switch over to full-time musculoskeletal medicine. I chose the latter as I felt that my patients needed an alternative to the usual medical approach to musculoskeletal pain, and to the “other” alternatives such as chiropractic or physiotherapy.

Concurrently, there were professional colleagues who influenced me with their research into the causes of musculoskeletal pain, notably Professor Nik Bogduk, and the various doctors who had already gone into full-time musculoskeletal medicine. Drs Clive Kenna, David and Vern Vivian in Melbourne, Gordon Byth and Karl (“Chippy”) Rotkirch in Brisbane, Jeff Phillips in Toowoomba, and others were some of these. Dr Ron Palmer and I decided to start a dedicated spinal medicine clinic opposite the Royal Brisbane Hospital, as well as my continuing to work in a blended practice in Sandgate.

Having made the decision to “jump” into musculoskeletal medicine, there were consequences – the most significant being that I had put myself outside of the “usual” general practice model. This was the same experience for Drs Vic Wilk and Steve Jensen in Melbourne, Dr Margi Taylor in Adelaide, and Dr Iain Hewitt (RIP) in Perth. Soon after came Drs Peter Jackson, Philip Watson, Robert Liong and Bob Michael in Brisbane and others also became full-time musculoskeletal medicine practitioners.

Currently, there are many non-specialist, according to AHPRA, full-time musculoskeletal medicine practitioners in Australia who have “taken the leap” out of general practice. Why mention this? It is partly to give some background to the establishment of musculoskeletal medicine as a full-time endeavour

amongst those of us who would have otherwise been GPs.

The other reason is to highlight the role that these non-GP/non-specialist doctors perform in the life of the AAMM. It is often those doctors who are involved in the executive roles of the organisations such as the AAMM and the Australasian Faculty of Musculoskeletal Medicine. Without their efforts, a good deal of momentum would be lost in promoting this as a separate medical speciality. Naturally, there are many who are not full-timers who fulfil executive roles in the Association and they deserve recognition for their efforts as well.

My hope is that eventually, there will be a recognised specialty of musculoskeletal medicine in this Australia as has occurred in New Zealand. Our patients certainly deserve this. Without the eventual establishment of such a specialty the teaching of the musculoskeletal medicine paradigm will also probably grind to a halt.

The surgical, rheumatological, sports, and rehabilitation paradigms are not the same as the one we follow especially when it comes to assessing and treating non-surgical musculoskeletal pain problems. All have their place – and so do we.

Don’t forget the upcoming annual scientific meeting to be held in October. The program is being finalised and there will be email notification coming out to all members soon. I hope that EVERYONE can make it to what promises to be an informative and enjoyable weekend.

This will be my final report in the AMM Journal – at the AGM in October I will be standing down as president and I would encourage you to consider how you might contribute to the AAMM. Thanks to all of my committee members who have helped over my term and I trust the Association has benefited from my efforts as president.

See you at the conference.

*- Geoff Harding*

# From the NZAMSM President

September 2012 saw the release of the document “Fit For Work? Musculoskeletal Disorders and the New Zealand Labour Market”.<sup>1</sup> The executive summary of this said: “Musculoskeletal disorders (MSDs) are currently the leading cause of disability in New Zealand. Among the working age population they are the second largest category of conditions resulting in sickness and invalid’s benefit payments and are thought to make up a large proportion of workers’ compensation claims.”

Despite the significance of MSDs, globally, medical schools allocate less than 10% of their curriculum to musculoskeletal medicine and New Zealand is no exception. This was discussed in the NZMJ editorial by Jean-Claude Theis<sup>2</sup> who was of the view that “Curriculum committees allocate teaching time not based on educational evidence but influenced by the opinion of some powerful heads of department who argue strongly for their disciplines. This has led over the years to distortion of medical curricula to the detriment of disciplines such as orthopaedics, rheumatology, sports medicine, rehabilitation etc.”

It is no surprise then that doctors who leave the hospital setting and commence practice in the community are unprepared for either the volume (conservatively estimated at 15% of general practice consultations)<sup>3</sup> or the spectrum of musculoskeletal conditions in the community. One would think that faced with this yawning chasm between their training in musculoskeletal medicine and the clinical reality that doctors would seek to redress this deficit. In reality they do not. This behaviour is explained by Regehr and Mylopoulos<sup>4</sup> “The first assumption implicitly present in our current conceptualization of the self-regulating professional is the assumption that professionals reflect on performance data for the purpose of exposing gaps in knowledge. Research, however, has placed the strength of this assumption in doubt. Instead, studies have shown that people will often reinterpret data that would be evidence of poor performance in ways that reinforce their self-concept as competent professionals.”

It seems we delude ourselves about our medical competence, and musculoskeletal disorders are no exception. Furthermore MSDs are generally about morbidity not mortality, so it is possible to avoid the reality check that the death of a patient provides.

While one of the objects of the constitution of the New Zealand Association of Musculoskeletal Medicine (2. d) is “To

promote the teaching of musculoskeletal medicine and manipulation to undergraduates in medicine as well as to postgraduates”, it is a major challenge to get the attention of our colleagues in New Zealand who have their energies focused on the laudable public health issues of reducing the mortality from disease.

In New Zealand, the Primary Health Organisation (PHO), the funding agency which provides continuing medical education (CME) in primary care (at no charge to the participants) like the medical schools does not focus on MSDs. In replicating the pattern of medical school education, those in the PHO will find no objection from their captive audience, as Regehr and Mylopoulos<sup>4</sup> explain “... health professionals more often attend continuing education sessions that reinforce what they already know.” The need to achieve targets for immunisation, cancer and cardiovascular screening so as to maximise income understandably focuses our colleagues’ attention on being up to date in managing these conditions which are the bulk of the CME provided by the PHO.

Until similar financial signals are given for the management of MSDs it is hard to see a change in our colleagues’ behaviour in the near future.

Meanwhile the conditions for a perfect storm are developing. The tax base to pay for our public health system and our superannuation derives from our economy. One of the drains on the economy is musculoskeletal injuries, which are responsible for at least 90% of occupational injuries and which comprise the second largest category of conditions resulting in sickness and disability benefits, and yet educating the medical workforce on musculoskeletal diagnosis and rehabilitation is given no priority as judged by the time allocated to MSDs in our medical schools and by our PHOs. Nothing more it seems is being provided for the management of the inevitable increase in musculoskeletal conditions that will accompany the longevity from the public health measures being instituted or address the fact that raising of the age of eligibility for superannuation will mean a longer time till those working to reach superannuation. The plain fact is that acquiring new knowledge is difficult and requires effort to put it into practice. Even with the best will in the world only about a third of practitioners will have changed their practice 1-2 months after attending CME.<sup>4</sup> Fordyce, the pioneering clinical

psychologist in pain, was scathing about the ability of information to alter behaviour, stating “Information is to behaviour as spaghetti is to a brick”.

Having exposed the illusion of traditional continuing medical education, Regehr and Mylopoulos make the point that “much of an experienced practitioner’s daily practice has less to do with solving problems than with remembering solutions.” Faced with a novel problem, the need to discover “a solution for this patient is not only an opportunity to help this patient, but also an opportunity to improve future practice: an opportunity to learn. Sometimes this learning involves simply the accrual of new facts such as the dosage of a particular drug or the Latin name for an uncommon disease. At other times it might have the potential to invoke a radical shift in understanding regarding some aspect of practice, a sudden understanding that colors the conceptualization of future cases and past ones alike.” If we are to achieve the object of the NZAMM and promote the teaching of musculoskeletal medicine and manipulation to undergraduates in medicine as well as to postgraduates we need to acknowledge the deficiencies of current CME and to again quote Regehr and Mylopoulos “by shifting our perspective from a focus on education to a focus on learning, we will be able to direct additional efforts at understanding how professional learning not only arises from practice, but actually occurs in practice and is informed by practice”, that is, this approach marks a change from didactic learning to recognising the importance of “learning on the job” and the importance of hands-on workshops as well as plenary sessions at conferences.

When we are asked to provide musculoskeletal education to our colleagues, it raises the question of how do we avoid the didactic approach and foster true learning?

*- Mike Clearly*

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# Musculoskeletal medicine in Australia: A 50-year journey and perspective

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## Overview

As a septuagenarian reflecting on a medical career of over 50 years, I remain firmly convinced of the primary and key role of doctors, especially general practitioners, in physical and procedural musculoskeletal medicine (MSM).

During my time in over a decade of rural general practice I said many times that I could not have managed effectively without the knowledge and associated skills of manipulative medicine and all that emanated from it. This conviction and philosophy developed from experiences (outlined in this paper) prior to studying medicine.

The journey has been controversial and stressful at times but counterbalanced by the many rewards. My approach has modified over the decades and these changes and the reasons for them will be presented

## The background

My initial significant experience was that of recurrent thoracic back pain with referral to various parts of the thorax following childhood polio and subsequent kyphoscoliosis. Many years later when I was visiting a masseur/osteopath for a football ankle injury he asked me about my back problem and claimed confidently that he could alleviate the pain. I was cautiously skeptical as he deftly “cracked” my thoracic spine, and after a few days I realised that my long-term niggling back pain was much improved.

The seed of curiosity was sown. Then I observed relatives and sporting colleagues obtaining relief, sometimes dramatically, at the hands of spinal manipulators, including household names such as Mitchell, Saunders, and McAllister. While working as a GP registrar I was overwhelmed by the stream of patients with spinal pain and felt frustrated by my inability to deliver relief to the extent achieved by some chiropractors

and self-taught therapists. My supervisor then arranged a teaching session with Ed Allchin, a former rural GP working in Clayton. His rooms overflowed with people from all over Victoria – such was his reputation – and I observed his simple skills which were similar to Mitchell and McAllister.

My next revelation was as a surgical registrar at a Base Hospital where the general surgeon and orthopaedic surgeons were renowned for their successful management of back problems. To my amazement I found that it was through manipulation under general anaesthesia (GAMP) and I was able to observe and eventually treat via my own surgical lists. Considering their recalcitrant cases the results were outstanding.

## Rural general practice

I was now ready for rural practice which, as a former solo practice servicing about 2000 patients and with a modern bush nursing hospital, was ideal. Furthermore, my medical wife was proficient with anaesthetics. However, in due time I became aware that GAMP was not necessary although ideal for sub-acute or chronic pain in the “locked” spine of a tense patient. The challenge was to become skilled at basic office therapy and develop refined and diverse techniques according to the problem.

I was pleased to learn about the existence of an Australian Association of Musculoskeletal Medicine (AAMM) run by Frank May and other experienced wise heads and I was soon attending their annual meetings and learning “tricks of the trade”. James Cyriax, the medical guru of MSM attended one of the conferences and I was able to travel to London to attend his course. His cervical techniques were rather frightening and one could eliminate some of them from the repertoire. One particular

highlight of this exposure and the laying on of hands was the expertise acquired in the art of physical examination and the ability to “feel” soft tissue trouble spots in the back and neck.

Soon my practice was overwhelmed by people from all corners wanting to visit “the doctor with the magic hands”. Nothing magical really except that patients preferred a medically trained person providing fewer treatments to get results.

The reality struck me that I was now was a type of specialist in spinal pain medicine and that physical therapy had limitations and so it was necessary to develop other therapies. These included neurofasciotomy (aka rhizolysis by the founder), epidural injections, facet joint injections, acupuncture, and prolotherapy.

The first decade could be summed up by the following lessons and strategies of management learned from the practice of physical medicine:

- reduced status of cervical manipulation with replacement by the safer and effective muscle energy therapy
- importance of paying attention to “red flags”
- increased awareness of spinal dysfunction syndromes especially headache, chest pain, and leg pain
- improved ability with physical examination and ability to sense pathology
- the amazing results of manipulation for the thoracic spine
- excellent outcomes of stretching (traction) (not manipulation) under GA for a “locked” or stubborn dysfunction of the cervical spine
- lumbar GAMP for a similar clinical problem with the lumbosacral spine
- the necessity to employ ancillary pain-controlling therapies
- the importance of patient education including handouts and exercises
- the value of working in a team including orthopaedic surgeons,



rheumatologists and physiotherapists or other appropriate allied health therapists.

## Spinal manipulation workshops

It became apparent that the best way to promote our skills was to run national workshops in spinal mobilisation and manipulation. The RACGP approached me to consider this since by now AAMM was being influenced by people from rehabilitation medicine and who were less interested in general practice. Dr Clive Kenna, a very perceptive MS physician and graduate of manipulative physiotherapy, agreed to join with me to conduct courses in back pain and spinal manipulation around the country, with the focus on the rural GP who had a huge workload in this area. The courses attracted considerable angst but were very successful and participants are at the forefront of the art in Australia. Unfortunately it was not sustainable as I moved into full-time academia and later developed the physical wear and tear of almost 40 years of physical therapy. It would be marvelous if these workshops in MSM skills could be rejuvenated.

## Concluding remarks

My now limited practice is virtually 100% MSM but with an emphasis on procedural work for problems such as trigger finger, carpal tunnel syndrome, joint inflammation,

and soft tissue tendonopathy. Our members while maintaining the faith and skills in spinal therapy should develop expertise in this injection therapy. With time and some wisdom I would recommend a more conservative approach to the enthusiastic spinal manipulation that marked those early days.

Current recommendations can be summarised thus:

- in the light of recent knowledge of tendon and ligamentous healing promotion of exercises especially stretching for the spine and also soft tissue injuries such as plantar fasciitis, tennis elbow and anterior knee syndrome
- muscle energy therapy for the neck with minimal use of manipulation
- basic proven office manipulative techniques for the common mechanical disorders of the thoracic and lumbosacral spine
- under general anaesthesia gentle manipulation of the lumbosacral spine for recalcitrant problems and controlled traction of the neck with counter traction.

Members should not be discouraged by the rather modest findings and recommendations for spinal manipulation from evidence-based medicine. The studies are generic and do not allow for the special skills of highly successful therapists who achieve outstanding individual outcomes. I believe this also applies to acupuncture where some therapists achieve outstanding success while some of us seem to lack the special charisma, skills, and experience of the eminently successful ones. It is

great for our suffering clientele that GPs can incorporate these MSM skills into comprehensive general practice.

The future is good if we continue to confidently practice our art within this context and continue to learn from each other through meetings and workshops.

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# CT-guided ozone nucleolysis (ONL) in the management of back pain and sciatica

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## Introduction

Back pain is an enormous clinical, social and economic problem, with up to 85% of adults experiencing back pain at some stage during their lifetime.<sup>1</sup> Chronic low back pain has many causes that can generally be divided into degeneration of the intervertebral discs (39-42%), facet joints (31%) and sacroiliac joints (18%).<sup>2,3</sup> Although disc disease is implicated in all ages, sacroiliac and facet joint arthropathy are more frequently seen in older patients.<sup>2</sup>

Historically, after failed conservative treatment, surgical intervention has been the next therapeutic option. The Maine Lumbar Spine Study, where most patients in the surgical arm received open discectomies for lumbar disc herniation with sciatica, showed significant benefit of surgery over conservative management in patients with moderate or severe sciatica. This relative benefit of surgery unfortunately decreased over the five-year period studied,<sup>4</sup> with a failure rate variably quoted between 10% and 40% ("Failed Back Surgery Syndrome").<sup>5</sup> Five-year re-operation rates are estimated at approximately 14%, with half occurring within the first post-operative year and success rates declining dramatically with every re-operation.

Since the 1980s, many minimally invasive percutaneous methods have been developed as a means of obviating surgical intervention, delaying surgery or decreasing the number of surgical interventions required. These minimally invasive interventions include percutaneous endoscopic or laser discolysis, intradiscal electrothermy (IDET) and chemonucleolysis. Studies involving these procedures have been mostly cohort studies and have limitations.<sup>15,16</sup> Despite insufficient evidence for routine use, specific subgroups of patients have shown discernible benefit with these interventions.<sup>6</sup> Ozone nucleolysis (ONL)

has recently shown promise in a similar cohort/subset of patients who have failed conservative treatment and are keen to avoid surgery. It is also a minimally invasive injection therapy that is typically provided in an ambulatory/outpatient setting. ONL has the advantage that it can be used in both contained and non-contained herniations, unlike other percutaneous techniques, such as alcohol, chymopapain or thermal ablation, which can have deleterious effects upon adjacent neural structures.<sup>7</sup>

## Intervertebral disc pathophysiology

As the intervertebral disc degenerates with age, fissures of the rigid outer annulus fibrosis occur, with secondary herniation of the nucleus pulposus. In the normal disc, only the outer annulus fibrosis receives sensory innervations; however, these nerves may penetrate deeper into the disc following annular degeneration and fissuring. The proteoglycan content of the nucleus, having not been exposed to the immune system after birth, triggers an autoimmune reaction,<sup>8</sup> inducing pro-inflammatory mediators, which excite and sensitise nociceptors to bradykinin and other pain-producing substances. Further to this, non-immune mediated infiltration of histiocytes, local fibroblasts from the disc periphery and chondrocytes within the disc, result in the production of cytokines, interleukins 1 and 6 and tumour necrosis factor-alpha, ultimately leading into an accumulation of phospholipase A2, prostaglandin E2, matrix metalloproteinases and thromboxanes. These substances result in an inflammatory cascade which further sensitise local nerves as well as the dura and surrounding spinal nerves.<sup>8-10</sup>

Phospholipase A is an important mediator

of radicular pain, which in itself is responsible for liberation of arachidonic acid. The inflammatory cascade results in increased tissue swelling, with secondary decreased arterial supply as well as increased venous and lymphatic stasis.<sup>7</sup> The net ischaemic effect of decreased oxygen diffusion, increase in local lactate concentration and decrease in pH results in a vicious cycle of increased swelling and promotion of inflammation, which when it exceeds a certain threshold, results in direct mechanical compression of neural structures such as spinal nerves, small nociceptive fibres in the posterior annulus fibrosus, posterior longitudinal ligament and ventral dura that can all lead to chronic pain.<sup>11-13</sup>

## Ozone mechanism of action

The unstable ozone molecule (O<sub>3</sub>) consists of three oxygen atoms covalently bonded to one another, with a molecular weight of 48 kDa. Ozone must be administered at non-toxic concentrations of 1-40 µg, where ozone has the paradoxical effect of inducing endogenous production of antioxidant enzymes in tissues without overcoming their antioxidant mechanisms. In excess of this, the antioxidant enzyme system is overwhelmed, with the result being accumulation of superoxide anion (O<sub>2</sub><sup>-</sup>) and hydrogen peroxide, which can cause cell membrane degradation. Ozone dissolves in intradiscal water and quickly dissociates into an oxygen molecule (O<sub>2</sub>), thereby releasing an oxygen free radical. This free radical gives ozone its highly oxidizing property, upregulating intracellular antioxidant scavenger systems<sup>14</sup> and neutralizing excessive reactive oxygen species. As such, ozone

possesses powerful anti-septic properties, as well as immunomodulating, analgesic and anti-inflammatory characteristics. It exerts a direct effect on complex macromolecules, inducing degeneration of proteoglycans and glycosaminoglycans within the nucleus pulposus by disrupting their intra and intermolecular chains, leading to collapse of their three-dimensional structure. The degradation of these macromolecules releases entrapped water that is then reabsorbed, thereby dehydrating the disc and reducing its volume. This dehydration and loss of discal volume, with decreased mass effect upon surrounding structures, is felt to be the main mechanism of action by which ONL improves the symptoms of radiculopathy. The cellular degeneration of the matrix is then replaced by connective and activated fibroblasts within five weeks, causing additional scarring and further reduction of the herniated disc, with vacuole formation and fragmentation on histological examination, a process referred to as “disk mummification”.<sup>15</sup> Extrinsic to the disc, ozone is known to have an immunomodulating effect, reducing the release and activation of inflammatory mediators such as cytokines, bradykinins, prostaglandins and other pain-producing substances. Ozone may also improve local oxygenation by increasing arterial afferent supply, venous and lymphatic stasis and reducing local acidosis.

## Ozone nucleolysis injection technique

ONL involves the direct injection of a mixture of oxygen and ozone into the intervertebral disc, using either fluoroscopy or computed tomography (CT) for guidance. The mixture can also be injected into the epidural space, intervertebral foramen and paravertebral muscles to achieve a further “halo” analgesic effect, depending on the anatomic abnormalities on imaging, clinical findings, available scientific evidence and individual operator experience. Like any gas, the ozone injected during ONL is visualized as an area of lucency and is best seen with CT, where even the smallest gas locule of ozone can be detected. CT accurately demonstrates the pattern and extent of spread within the disc, achieving a discographic effect, as well as any spread external to the disc should it extend beyond it. CT also has the advantage of three-dimensional appreciation of needle position, improved appreciation of spread of the ozone gas in relation to surrounding anatomic structures,

as well as decreased operator radiation exposure. Fluoroscopically guided ONL has been used with equal efficacy as when compared to CT and the techniques used to negotiate the needle into the disc are similar. Ultimately, determining which modality is used to perform ONL will vary with personal operator preference, experience and availability of the specific modality within the facility where the procedure is performed.

No specific preparation is required for ONL, with the procedure performed on an outpatient basis. Formal informed consent is obtained and the patient may be administered a light sedative and oral analgesics. Another alternative used at other institutions is to administer conscious sedation. At our institution, the patient is placed prone in the CT scanner (Emotion 16 slice Multi-detector CT, Siemens Medical systems, Erlangen, Germany) with a series of planning axial scans at 3 mm slices performed at the intervertebral disc level of proposed intervention. The intended needle trajectory is then planned from these images and the needle entry point marked on the skin. 5ml of 1% lignocaine is injected into the skin and subcutaneous tissues and thereafter, utilising a transforaminal approach, a 9 cm, 12.7 cm or 17 cm 22 g spinal needle is advanced into the affected disc under CT guidance at approximately 45-60°. As with any percutaneous disc injection, extreme care is taken to avoid contacting the exiting nerve root by visually following its path on the CT images during the procedure, as well as clinically monitoring the patient for any symptoms of leg pain. Once needle position in the disc has been confirmed (Figure 1A), a small amount of iodine contrast may be injected to outline the pattern of contrast spread, which typically predicts the spread of the ozone gas (Figure 1B). However, this step is often not performed and can be omitted. 5 cc of an oxygen-ozone mixture, prepared from room air using an ozone generator with a concentration of 30 µg/ml is injected (Figure 1B), at which point a set of three axial images is obtained (one above, one at and one below the level of injection). The needle is withdrawn to the level of the foramen, where contrast is injected (Figure 1C) so as to avoid any intravascular injection of ozone and to confirm epidural spread. Once confirmed, 2 cc of celestone chronodose, 5 cc of 1% lignocaine and a further 5 cc of ozone at a similar concentration as above are injected (Figure 1D). This technique is repeated for each level that requires treatment. The procedure is thus completed and the patient is rested in recovery bay for an hour and

*Figure 1A. Under CT-guidance, a 22 g spinal needle is negotiated into the periphery of the nucleus pulposus of the L4/5 intervertebral disc, approaching the disc from the left side. The centre of the nucleus pulposus is indicated by the arrow.*



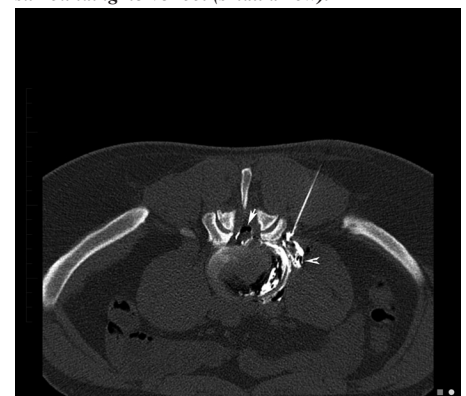
*Figure 1B. Contrast is then injected, denoted by the hyperdense (white) fluid within the disc, followed by the ozone gas (hypodense, or dark material; long arrow). In this instance, gas is already seen in the epidural space, highlighting a focal left paracentral protrusion (short arrow).*



*Figure 1C. The needle is then withdrawn to the neural foramen and contrast injected, with its flow observed (arrow), confirming an extravascular position.*



*Figure 1D. A further dose of ozone is injected, with extension of the gas into the epidural space (long arrow) as well as the neural foramen and surrounding nerve root (small arrow).*





typically discharged following this time frame without event. A week of rest is prescribed, with continuation of an analgesic regimen familiar to the patient. Following this, rehabilitation may commence and review with the referring clinician.

## Ozone nucleolysis (ONL) efficacy

In a meta-analysis of 12 studies, ONL demonstrated an 80% likelihood of improvement in over 8,000 patients, similar to results seen in surgical discectomy, with a low complication rate of 0.06% and improved recovery time.<sup>16</sup> Apart from the advantage of being minimally invasive, ONL minimises epidural fibrosis/scarring, is a quick and simple procedure, requires at most only light sedation and, where required, can be repeated numerous times at multiple levels. It is also of advantage in patients who pose an unacceptable anaesthetic risk. The comparable efficacy of ONL and microdiscectomy was further supported in a series of 45 patients with non-contained lumbar disc herniations. Twenty-seven patients (90%) in the ONL group showed a statistically significant improvement in pain and function that was similar to the microdiscectomy group (14 patients; 93.3%). Owing to “aggravating” symptoms, two patients from the ONL group underwent subsequent surgery.<sup>17</sup> Similar success was noted between ONL and microdiscectomy cohorts, with patients proceeding emergently to microdiscectomy in the first instance only in the context of severe pain and/or neurological deficit.<sup>18</sup>

In an observational study of 2,900 patients, ONL and intraforaminal zone injections were effective for soft disc herniations (75-80%), multiple herniations (70%) and failed back surgery syndrome (55%), without complications.<sup>19</sup> The same authors published similar results for 2,200 patients, with again high success rate of 80% at six months, which dropped slightly to 75% at 18 months. The failure rate was higher in patients with spinal canal stenosis, calcified herniated disk, recurrent herniation with epidural fibrosis and lateral recess herniation.<sup>20</sup> Excellent results were also observed in a group of 600 patients, where a 78.3% success rate was noted in patients treated with ozone therapy and periganglionic steroid injection, compared with a 70.3% success rate in those treated with ozone therapy alone. In a group of 621 patients who were subjected to CT-guided ONL in combination with periradicular infiltration with steroids, the Oswestry Disability Index (ODI) and visual analog

pain scale (VAS) were measured. In this study, it was observed that patients younger than 50 years had significantly better values on the VAS and in ODI scores.<sup>21</sup> Combined ozone and steroid intradiscal and intraforaminal injections have been shown to be more effective (74% success rate at six months) than steroid alone (47%).<sup>22</sup> ONL has also demonstrated an additional benefit when combined with radiofrequency ablation (RFA) of the nucleus pulposus (VAS of 26 for ONL/RFA combined, compared to 33 in ONL alone at 12 months; ODI of 21 and 26 for ONL/RFA and ONL alone respectively) and though an exciting combination of pain management procedures, this has only been reported in one study and further research is required.<sup>23</sup> ONL has also been used with collagenase and shown to have comparable results to surgery.<sup>24</sup>

## Other uses of ozone

In a randomised control trial, ozone injections into the neural foramen alone were shown to be of improved efficacy in the management of lower back pain and/or sciatica versus steroid injections alone at six months (74% versus 58%).<sup>25</sup> Intramuscular paravertebral injections of ozone also resulted in a lower VAS (0.66) versus the control sham group (4.00) who received simulated therapy. Furthermore, 61% versus 33% of patients became pain free. Ozone therapy was also associated with a shorter period of non-steroidal anti-inflammatory therapy.<sup>26</sup>

### Indications

- Lumbar and radicular pain not responding to conservative treatment
- Imaging features that account for/are concordant with the clinical presentation
- Poor surgical candidate
- Facet joints and paravertebral muscle spasms
- Contained and non-contained disc herniations
- Multiple levels
- Failed back syndrome

### Contraindications

- Pregnancy
- Sepsis
- Cauda equina syndrome
- Worsening neurological/motor deficit
- Migrated (sequestered) disc fragment
- Tumour
- Fractures

## Complications

Ozone therapy for lumbar disc herniation is a procedure that is safe, well tolerated and with a high success rate, making it appealing to patients as an alternative to surgery, or a palliating procedure where surgery has previously failed. Complications are fortunately rare, with minimal, or no, adverse effects at concentrations used for therapeutic application (10-40 µg/mL). General complications not specific to ozone but common to all percutaneous injections include septic complications such as cellulitis, discitis, epidural abscess and septicaemia.<sup>27</sup> The use of pre-procedural antibiotics as well as using a co-axial needle technique are means by which the septic complication rate may be decreased, though this is a known contentious issue in discography. It has been postulated that the disinfecting properties of ozone may decrease the chances of septic complications following percutaneous ONL.<sup>28</sup> It is postulated that microfractures within the disc may communicate with the spinal canal and thecal sac, resulting in transient though rapid increases in CSF pressure and thus account for rare neurological complication such as blindness (due to bilateral vitreo-retinal haemorrhages,<sup>29</sup> stroke<sup>30</sup> and nerve trauma,<sup>31</sup> though the latter may also occur due to direct needle trauma and/or post-injection haemorrhage/haematoma. The development of acute thunderclap headache<sup>32</sup> has been known to occur due to pneumocephalus as a consequence of inadvertent puncture of the thecal sac. Though not a complication per se, exacerbation of pain is a known issue following the procedure that typically settles within several days and requires rest, avoidance of exacerbating activities and analgesia.

## Criticisms of ozone-based percutaneous therapies

Many ONL and non-intradiscal ozone spine injection studies to date have included heterogeneous patient groups with the diagnosis of “back pain/lumbago” or “sciatica” and for which a broad range of treatments have been prescribed. Most studies have compared ONL injections, with or without periradicular/foraminal cortisone and/or ozone injection, as well as paravertebral injections of ozone. Further to this, few studies have performed follow-up CT and/or MRI examinations documenting the resolution/improvement



of disc pathology occurring in conjunction with clinical improvement. Admittedly, this may be time consuming in practice and adds expense to patient management. Naturally, given the proposed mechanism of ONL, ozone therapy works first and foremost at the cellular level, reducing inflammation and therefore potentially resulting in clinical resolution of symptoms with decreasing disc volume. Hence, many patients may improve simply on the basis that the inflammatory component of their back pain has resolved, despite unaltered disc volume.

The current approach at our institution has been with an open mind when it comes to ozone-guided therapies. As it is a promising technique with minimal complications and is currently finding broad applications, many clinicians and patients are keen to trial ONL as a primary treatment, following failed cortisone injections, as a palliative procedure or as a final procedure in an attempt to avoid surgery. Hence, we see a heterogeneous group of patients in whom ozone has been injected with great success; however our success thus far has been anecdotal. We do not feel it unreasonable to use ozone in similar indications as one would use cortisone (for example, an epidural or intraforaminal/periradicular injection) and obviously where a concomitant disc herniation or bulge is present, then ONL can be performed in the same sitting. In our experience, we have found this technique has worked the best. We do not perform ozone paravertebral muscle injections, namely because this has never been referred to us and also possibly due to the fact that, where this is being performed, the procedure is performed clinically and thus radiological guidance is not required.

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# An evidence-based approach to human dermatomes\*

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**Abstract.** The dermatome is a fundamental concept in human anatomy and of major importance in clinical practice. There are significant variations in current dermatome maps in standard anatomy texts. The aim of this study was to undertake a systematic literature review of the available evidence for the distribution of human dermatomes. Particular emphasis was placed on the technique of ascertainment, the location and extent of each dermatome, the number of subjects studied, and methodologic limitations. Our findings demonstrate that current dermatome maps are inaccurate and based on flawed studies. After selecting the best available evidence, a novel evidence-based dermatome map was constructed. This represents the most consistent tactile dermatomal areas for each spinal dorsal nerve root found in most individuals. In addition to highlighting the orderly arrangement, areas of consistency and clinical usefulness of dermatomes, their overlap and variability deserve greater emphasis. This review demonstrates the validity of an evidence-based approach to an anatomical concept. *Clin. Anat.* 21:363–373, 2008. © 2008 Wiley-Liss, Inc.

Key words: dermatome; spinal nerve; dorsal nerve root; human

## Introduction

A dermatome is typically defined as the cutaneous area supplied by one spinal nerve, through both rami (Standring et al., 2005). Alternative definitions include the cutaneous area supplied by a single posterior nerve root and its ganglion (Haymaker and Woodhall, 1953; Bonica and Loeser, 2001) or one spinal cord segment (Schuenke et al., 2006), or the tissue within a somite that forms part of the dermis (Anthoney, 1994). The dermatome is a fundamental concept in human anatomy highly relevant to clinical practice. In neurology and orthopedics, dermatomes are a key factor in the clinical diagnosis of radiculopathy due to a prolapsed intervertebral disc or other causes (Rodriguez et al., 1987; Gagnard-Landra, 1996), in determining the level of spinal cord injury, and in the intraoperative monitoring of nerve root and spinal cord function by dermatomal somatosensory evoked potentials (Cohen and Huizenga, 1988; Toleikis et al., 1993). In anesthesiology, dermatomes are tested to determine the sensory limits of regional anesthesia such as before Cesarean section (Congreve et al., 2006) and in general medicine, knowledge of the dermatomal distribution of referred pain from visceral disease is an everyday tool in differential diagnosis.

Given the clinical importance of dermatomes, it is surprising that there is so much variability between dermatome maps in standard anatomical and medical reference texts. How were these maps constructed and on what evidence were they based? With this question in mind, we undertook an evidence-based systematic review of the location and distribution of human dermatomes.

## Materials and methods

The study consisted of three elements:

1. A detailed review of current standard anatomical reference and teaching texts identifying important major variations between dermatome maps.
2. A systematic literature review using Ovid Medline and the keywords skin, spinal nerve root, and dermatome. This was combined with an OvidSP Medline search using the terms dermatome and map. Similar searches were performed using the electronic biomedical database, PubMed, and the internet resource, Google Scholar. With the exception of a few frequently cited foreign

language articles, searches were restricted to English language papers. All relevant secondary references were retrieved. Each paper was studied independently by two researchers (ML and MDS) with particular emphasis on (a) the technique used to map the dermatome, (b) the location and extent of each dermatome and any reported variations, (c) the number of subjects studied, and (d) methodologic flaws. An attempt was made to grade the quality of the relevant evidence into one of three categories, using a scheme adapted from clinical medicine (Guyatt et al., 2006). Evidence was considered good (accurate methodology, further research unlikely to change the result, reasonable consistency in data, appropriate numbers of cases), intermediate (further research likely to change the result, deficiencies in methodology or sample size) or poor (very uncertain contribution).

3. Construction of a novel dermatome map using the best available evidence. This required the expert assistance of a professional medical illustrator (RM).

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# Results

## Current dermatome maps

Fourteen different dermatome maps were identified from a review of 13 texts (Abrahams et al., 2003; Agur and Dalley, 2005; Drake et al., 2005; Standring et al., 2005; Moore and Dalley, 2006; Netter, 2006; Palastanga et al., 2006; Schuenke et al., 2006; Sinnatamby, 2006; Snell, 2006; Saladin, 2007; Thibodeau and Patton, 2007; Marieb et al., 2008). Striking variations exist between these texts, examples of which are shown in Table 1. Occasionally, there are inconsistencies within individual texts (e.g., in *Gray's Anatomy* 39th edition the pattern of lower limb dermatomes depicted on the whole body dermatome map differs from that shown on the lower limb map). Almost all maps are based on two primary sources, namely Foerster (1933) and/or Keegan and Garrett (1948). However, both of these papers describe different dermatome arrangements (see below). Texts that reference Keegan and Garrett (1948) typically include C2 and thoracic dermatomes but these were not actually investigated by these authors. Although almost all authors note the concept of overlapping dermatomes, none of the dermatome maps actually highlight this.

## The evidence base

The various techniques used to study the location and distribution of human dermatomes are shown in Table 2. Each method of study has limitations. Nevertheless, an attempt was made to broadly grade the quality of evidence derived from each type of study according to previously defined criteria. The results of this analysis are best presented by considering the strengths and weaknesses of the three most frequently cited studies upon which most human dermatome maps are based before briefly discussing the limitations of other studies. These three clinical studies of patients are analyzed in order of their importance.

**Foerster's map.** Otfried Foerster, a neurologist and neurosurgeon at the University of Breslau (then in Germany), mapped the residual area of cutaneous sensation in humans after isolating single dorsal nerve roots by surgical section of at least two adjacent dorsal nerve roots both above and below (Foerster, 1933; Bumke and Foerster, 1936) (Fig. 1). Dorsal nerve roots were divided to relieve spasticity and pain, the latter principally from tabes dorsalis (Zulch, 1969; Tan and Black, 2001).

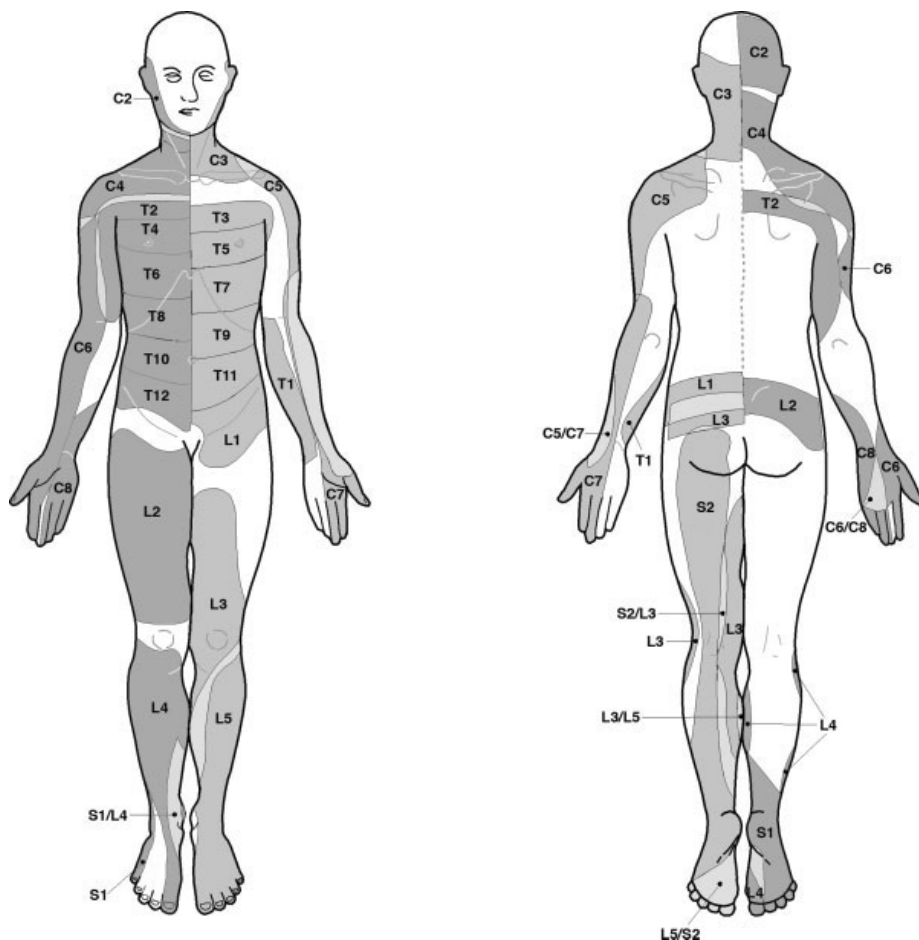


Fig. 1. Foerster's tactile dermatome map (Foerster, 1933; Bumke and Foerster, 1936). Drawn from Foerster's clinical photographs. The posterior aspect of thoracic dermatomes included only T2. Overlapping dermatome areas are shown in lighter shades.

Foerster did not discuss the rationale for a leaving single root intact in such cases other than for the experimental purpose of defining dermatome distributions, and thus the ethics of these procedures are questionable.

Foerster managed to isolate individual dorsal nerve roots for L1 to S2 inclusive, by dividing dorsal nerve roots above and below in two to four patients for each selected root level. However, cervical dermatomes were mostly assessed after sectioning dorsal nerve roots either above or below the selected root (C2–C5 and C8 in two to five cases each), thus obtaining the proximal or distal boundary, respectively; only C6 (one case) was determined using the isolation method. For C3–C5 and C8, these results were supplemented by assessing the area of cutaneous vasodilatation following electrical stimulation of sectioned dorsal nerve roots (Table 2). Foerster presented no data on C7 in his 1933 report but two patients in whom the upper border of C7 was mapped were included in his 1936 publication (Bumke and Foerster, 1936). Thoracic dermatomes were also studied in “a great number of cases” (Foerster, 1933). Although no individual data were given, S3, S4, and S5 were stated to supply the

perineum, anus, scrotum and penis (Bumke and Foerster, 1936).

In addition to mapping areas, Foerster confirmed in humans several additional important observations about dermatomes that had been made by Sherrington in his studies on monkeys (Sherrington, 1893, 1898): dermatome areas vary between individuals; except in the midline, adjacent dermatomes overlap to a large extent; tactile dermatomal areas are larger than those determined by pain and temperature sensation; with the exception of C2 there is no clinical sensory loss if only one nerve root is sectioned.

Foerster's studies can be criticized for having relatively few subjects, relatively poorly documented methods of testing and reporting, a lack of information about consistency of results, and failure to document the interval between root sectioning and testing. The latter affects the degree to which adjacent dermatomes compensate for sensory impairment (Richter and Woodruff, 1945; Cole et al., 1968) and the potential for nerve regeneration after sectioning. Nevertheless, his studies provide some of the best available evidence for dermatome distributions in humans.

**Head and Campbell's map.** Henry Head,



a physician at the London Hospital, based his human dermatome map on drawings or photographs of 450 patients with Herpes zoster skin eruptions (Head and Campbell, 1900) (Fig. 2). However, herpetic eruptions could only be linked to specific spinal nerves with certainty in a small proportion of cases. Indeed, histologic confirmation of single dorsal root ganglion inflammation was obtained in only 16 cases (C3, C4, T2, T4, T6-T8, T11, T12, and L1 roots in one to three cases each). Furthermore, no examples of C8 or S1 dermatome involvement were recorded.

Although the cutaneous distribution of the herpetic eruption could be recorded accurately, assumptions were often made about the exact dorsal root involved. Head and Campbell (1900) were aware of this potential problem but maintained that their histologic studies supported the overall accuracy of their map. They noted variation in the distribution of specific dermatomes between individuals by up to half a dermatome (especially on the limbs) and they acknowledged that dermatomes overlap.

It is now recognized that herpetic eruptions may affect several adjacent dorsal root ganglia (Lewis, 1958) and that not all cutaneous nerve fibers of a single dorsal root ganglion will necessarily be infected and show eruptive lesions, but the large overall sample size and selected histologic validation justify consideration of these data as an important contribution to the human dermatome map. Moreover, Head and Campbell (1900) uniquely described the dorsal thoracic dermatome pattern (T3–T12).

**Keegan and Garrett’s map.** This map which shows neat nonoverlapping bands running extensively down the limbs from the posterior midline was based on clinical cases of intervertebral disc prolapsed causing nerve root compression and diminished cutaneous sensitivity (Keegan and Garrett, 1948) (Fig. 3). The authors recorded hypoalgesia demonstrated by light pin-scratch (which they considered more reliable than light touch or pinprick sensation) but also noted the distribution of radiating pain (Keegan, 1947). They acknowledged that the areas of hypoalgesia they plotted (the “true primitive dermatome”) did not represent the complete cutaneous distribution of nerve fibers within a single nerve root and that dermatomes did overlap. They also correctly disputed Foerster’s assertion that division of a single nerve root produces no loss of sensation. Keegan and Garrett’s study included a large number of patients. Of 165 disc prolapses at C5-T1, compression of a single nerve root was verified at surgery in 47 (28%) and of 1264 disc prolapses at L3-S2, 707 (56%) were confirmed at operation.

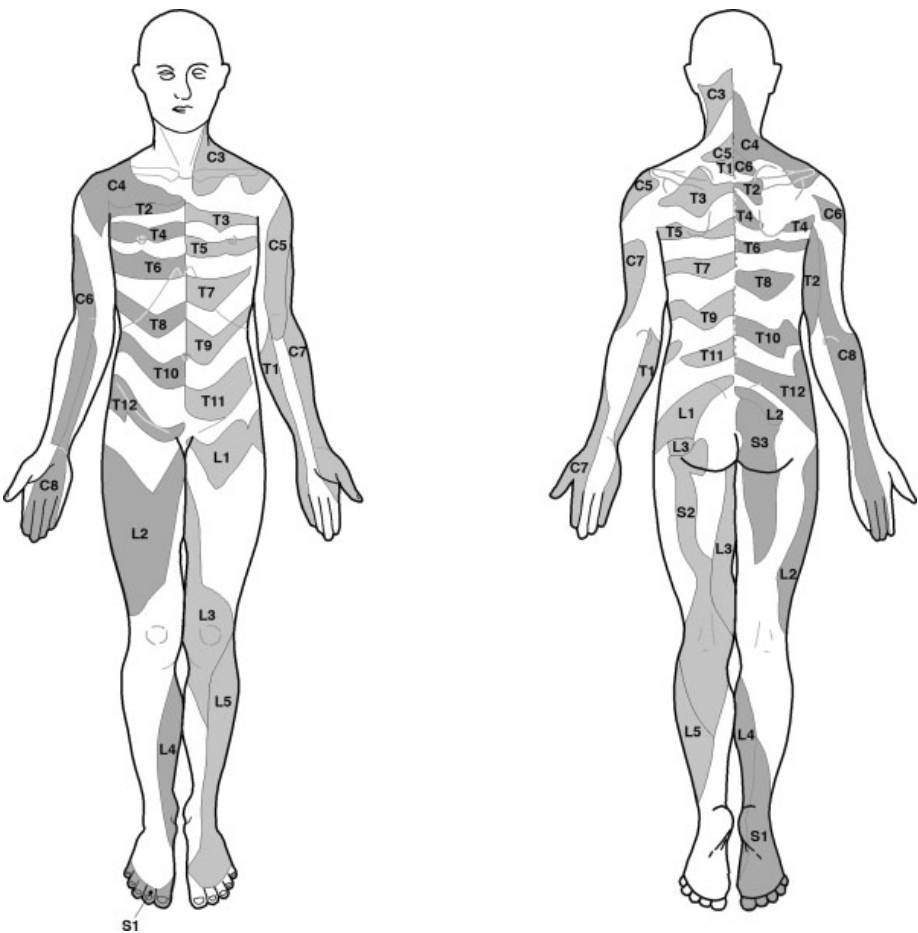


Fig. 2. Head and Campbell’s dermatome map (redrawn from Head and Campbell, 1900).

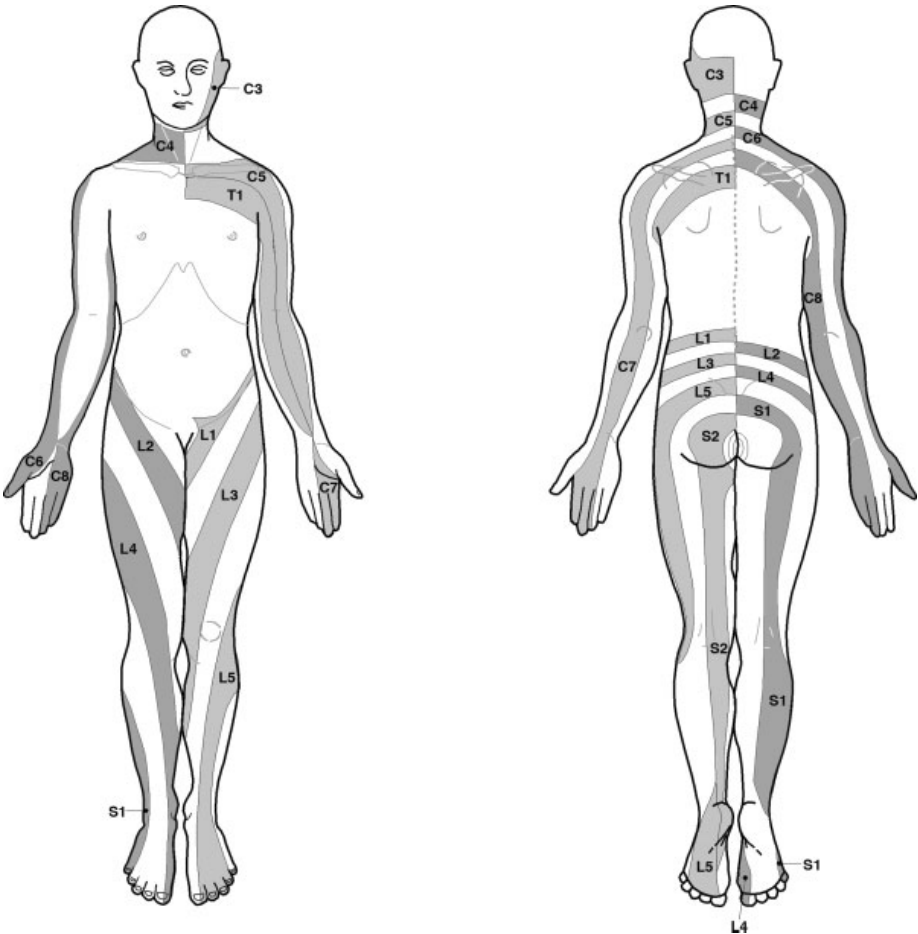


Fig. 3. Keegan and Garrett’s dermatome map (redrawn from Keegan and Garrett, 1948). Thoracic dermatomes were not studied by the authors and have therefore not been included.



Despite the widespread uncritical reproduction of the Keegan and Garrett map (see Table 1 for examples), it is the most flawed of the three core maps for several reasons. The majority of cervical root compressions were demonstrated by myelography only (being before the advent of accurate magnetic resonance imaging) and not confirmed at surgery. Some dermatomes were not assessed, e.g., L1 and L2, yet they appear in the chart. Only limb dermatomes were investigated—their representation of truncal dermatomes was derived from previous publications. The authors reported that areas of hypoalgesia in individual patients were highly reproducible and did not vary by more than a centimeter which is at odds with other reports (Falconer et al., 1947;

Davis et al., 1952). For example, Falconer et al. (1947) commented that mapping of root hypoalgesia after intervertebral disc compression was much less reliable proximally than distally.

Although a prolapsed intervertebral disc commonly compresses only one nerve root, more than one root may be affected (Davis et al., 1952). Incomplete compression of a single root can produce variable sensory loss (Falconer et al., 1947). Indeed, Keegan and Garrett (1948) noted that in some cases hyposensitivity was found only in the distal part of a limb but these cases were subsequently excluded from further comment. They were also concerned with explaining the embryologic basis of dermatome distribution in the limbs but dermatomes do not grow out from the

trunk with the developing limb bud as they supposed, rather nerves grow out from limb plexuses at a later stage of development to innervate specific target areas of skin (McLachlan, 1990).

Keegan and Garrett (1948) commented that they included in their analysis data relating to nerve root sectioning in 13 patients, and the results of radiologically guided injection of local anesthetic into lower cervical nerve roots in 10 medical students but exactly how these observations influenced their results is not clear.

A subsequent study by Davis et al. (1952) contradicted some of Keegan and Garrett's findings. They studied 500 patients with a prolapsed intervertebral disc, mostly the L4-5 or L5-S1 disc. Lesions were verified by myelography and surgery, and 327 of

**Table 1. Major variations in dermatome maps in seven standard anatomy texts limb<sup>d</sup>**

Title	Primary source of map	Dermatome map		
		Neck and upper limb <sup>b</sup>	Trunk limb <sup>c</sup>	Lower limb
Moore's Clinically Oriented Anatomy 5th edn. (2006)	Foerster (1933)	C7 includes middle three fingers rather than lateral three. T1 extends proximal to elbow. C3 extends further inferiorly.	Nipple—T4 Xiphisternum—not shown Umbilicus—T10	S1 includes lateral two toes rather than little toe only.
	Keegan and Garrett (1948)			
Netter's Atlas of Human Anatomy 4th edn. (2006)	Keegan and Garrett (1948)		Nipple—T4 Xiphisternum—T6 Umbilicus—T10 in one plate; T9/T10 in another	
McMinn's Colour Atlas of Human Anatomy 5th edn. (2006)	Keegan and Garrett (1948)	C3 extends further inferiorly.	Nipple—T4 Xiphisternum—T6 Umbilicus—T9/T10	T12 covers groin crease rather than L1. Hallux imprecise.
Last's Anatomy: Regional and Applied 11th edn. (2006)	Primary source not given but appears to be based on Foerster	C7 includes middle three fingers rather than lateral three. T1 extends proximal to elbow.	Incomplete	S1 includes lateral three toes rather than little toe only.
Gray's Anatomy for Students (2005)	Primary source not given but appears to be based on Foerster	C7 includes middle three fingers rather than lateral three. T1 extends proximal to elbow.	Nipple—T4 Xiphisternum—T5 Umbilicus—T10	
Gray's Anatomy 39th edn. (2005)	Cites Moffat's Lecture Notes on Anatomy (1993) which gives no primary source but appears to be based on Foerster	C2 extends over most of the neck.	Nipple—T4/5 Xiphisternum—not shown Umbilicus—T9/10	Whole body and lower limb dermatome maps differ. S1 includes lateral three toes rather than little toe only.
Grant's Atlas of Anatomy 11th edn. (2005) <sup>a</sup>	Keegan and Garrett (1948)	C3 extends further inferiorly.	Nipple—T5 in figure but T4 in surface anatomy photograph Xiphisternum—not shown Umbilicus—T10	T12 and L1 supply the groin crease rather than L1 alone.

a Only the dermatome map unique to this text is considered (not the reproduction of the dermatome maps depicted in Moore's Clinical Oriented Anatomy 5th edition).

b For the neck and limb dermatomes, differences between the primary source and the published map are highlighted.

c For truncal dermatomes, specific landmarks have been selected for comparison.

d Blank entries indicate no differences between primary source and published map.

the patients had sensory changes which were mapped by independent assessors using pinprick and light pin scratch. The areas of sensory loss associated with L5 or S1 root compression were very variable between individuals, and even showed some variation between assessors. Moreover, they could not demonstrate a narrow band of hypoalgesia extending from the spine to the distal end of the extremity as described by Keegan and Garrett (1948); over half of the patients with sensory changes had involvement of the leg and foot only. These findings were related to variability in the extent and location of the herniated nucleus pulposus lesion and variable nerve root compression (part of a dorsal root, an entire root, more than one root, involvement of a root higher or lower than expected). Consequently, Davis et al. (1952) were critical of charting dermatomes using clinical data from patients with prolapsed intervertebral discs.

Other authors have also been unable to reproduce Keegan and Garrett's proximal pattern of dermatomal sensory loss. Haymaker and Woodhall (1953) studied patients with prolapsed lumbar intervertebral discs. The dermatome fields were sometimes more extensive than those depicted by Foerster (1933) but they were unable to show the elongated proximal sensory loss reported by Keegan and Garrett. Similarly, using precise spinal nerve blocks, Bonica and Loeser (2001) could not demonstrate proximal extensions on to the anterior and posterior trunk for L3, L4, and L5 and roots C5-T1. Cole et al. (1968) studied tactile and pinprick sensation in a relatively large number of patients after complete section of individual nerve roots to relieve pain (26 patients after L5 division, 51 patients after S1 root section, and one patient after L4 section); they also found no evidence of the L4 or L5 dermatome extending onto the buttock and back. This lack of L4 and L5 representation on the dorsal aspect of the trunk (which contradicts Keegan and Garrett) is consistent with the detailed dissection study of Maigne et al. (1989). In a series of 37 human cadavers they were unable to identify dorsal cutaneous rami from L4 or L5. However, other authors maintain that cutaneous branches from L5 are conveyed via the inferior gluteal nerve and posterior cutaneous nerve of the thigh (Falconer et al., 1947), that L4 and L5 in some cases do in fact have dorsal cutaneous branches (Pearson et al., 1966), or that Keegan and Garrett's findings in relation to the proximal L4 and L5 dermatomes were due to a nondermatomal effect of radicular pain (Takahashi et al., 1995).

**Other studies.** A variety of other methods of mapping human dermatomes have been reported (Table 2). These methods differ in which neural structure was studied—the dorsal root, mixed spinal nerve, or spinal cord segment—and whether tactile, pain, or temperature sensation were assessed. Two more reliable methods in humans include the recording of mixed spinal nerve sensory action potentials after electrical skin stimulation (Inouye and Buchthal, 1977) and mapping the area of sensory impairment after local anesthetic spinal nerve block (Poletti, 1991; Nitta et al., 1993; Wolff et al., 2001).

Inouye and Buchthal (1977) studied 15 healthy volunteers by stimulating the skin of the digits using surface electrodes and recording sensory action potentials in mixed spinal nerves (C5–C8) using radiologically guided needle electrodes positioned just outside the intervertebral foramina. The technique had some limitations: not all spinal nerves were recorded in each case, there was a risk of volume conduction causing signals in adjacent spinal nerves, and they assumed that any articular afferents associated with stimulation of digital nerves would be conducted to the same spinal root as the dermatome. However, they established that spinal nerve signal patterns varied between individuals; the thumb received sensory innervation from C6, C7, or both, the middle finger from C7 and/or C8, and the little finger dominantly from C8 (although C7 could be stimulated and T1 was not recorded).

Nitta et al. (1993) studied 71 patients with lumbosacral radicular symptoms undergoing selective lumbar spinal nerve local anesthetic blocks (19 at L4, 41 at L5, 26 at S1). Nerve roots were first identified by radiculography under fluoroscopic control and areas of tactile sensory diminution were mapped. The accuracy of the technique, the number of subjects studied, and the results relating to consistency of the findings suggest that this study provides good evidence for those dermatomes studied. The authors confirmed considerable overlap between adjacent dermatomes and variation in sensory impairment between individuals. L4 and L5 nerve blocks produced some diminution in sensation across the buttock and posterior thigh similar to that described by Keegan and Garrett (1948) but only in less than half the patients. In contrast, S1 extended onto the buttock and trunk in 92% of cases. The areas of maximal consistency for the L4 and L5 dermatomes corresponded closely with Foerster (1933) but the S1 distribution was similar to Keegan and Garrett (1948). Considering that Head and Campbell (1900) had no cases of S1

herpes zoster eruptions and Foerster only two cases of S1 dorsal nerve root isolation, the evidence for S1 dermatome distribution from Nitta et al.'s study is likely to be significant. Furthermore, these findings for L5 and S1 are supported by Wolff et al. (2001) who investigated the distribution of hypoalgesia by pinprick testing in a smaller number of patients (L5=14, S1=11) after local anesthetic spinal nerves block and the distribution of parasthesiae after electrical stimulation of mixed spinal nerves in patients with chronic low back pain.

Both Nitta et al. (1993) and Wolff et al. (2001) evaluated mixed spinal nerves rather than dorsal roots. Ventral roots are known to contain afferent nerve fibers, some of which are pain fibers, although the function of others is uncertain (Hosobuchi, 1980). Thus, dorsal roots and mixed spinal nerves may differ in their cutaneous sensory supply. Another potential problem with the use of local anesthetic nerve blocks to evaluate dermatomes is that the anesthetic agent may diffuse and not remain precisely localized.

Poletti (1991) investigated C2 (n=6) and C3 (n=8) pain dermatomes by local anesthetic nerve block under fluoroscopic control. Hypoalgesia and analgesia were assessed by pinprick. Poletti's C2 and C3 pain dermatomes both fall within the overlapping C2 and C3 tactile dermatomal areas of Foerster (1933).

A variety of less reliable or relevant studies provide further insights into the pattern of human dermatomes (Table 2). Detailed studies in primates (Sherrington, 1893, 1898; Kuhn, 1953; Kirk and Denny-Brown, 1970; Dykes and Terzis, 1981), although strictly not comparable, have contributed to our general understanding of dermatomes and helped to complement human data. Anatomical dissection (Bolk, 1898) is limited by the ability to trace minute cutaneous branches and the difficulty of determining root values. In addition to nerve sectioning, Foerster (1933) investigated the area of cutaneous vasodilatation after electrical stimulation of the distal segment of divided dorsal nerve roots but whether this accurately reflects the area of the cutaneous tactile sensory dermatome is uncertain (Dykes and Terzis, 1981). Electrical stimulation of mixed spinal nerves within intervertebral foramina and recording of pain and parasthesiae produces a similar but distinctly different pattern to that of the cutaneous sensory tactile dermatome (Slipman et al., 1998; Wolff et al., 2001).

In our opinion, several techniques provide little valid evidence for the distribution of human dermatomes. Topical strychnine poisoning blocks inhibitory glycine

receptors in the spinal cord and its principal site of action is not the dorsal root ganglion (Frankenhaeuser, 1951). Spinal cord and cauda equine injuries provided some early insights into segmental sensory levels (Starr, 1892, 1894; Thorburn, 1893) but these data are unreliable for assessing spinal nerve dermatomes. Cutaneous afferents (in the rat at least) can descend by several segments after entering the spinal cord (cited in Greenberg, 2003). Techniques such as cutaneous thermography (Ash et al., 1986) and skin resistance (Richter and Woodruff, 1945), which depend on sympathetic innervation of the skin, are both inaccurate and inappropriate methods to measure cutaneous sensory dermatomes.

### An evidence-based dermatome map

After considering the available evidence, a novel dermatome map was constructed (Fig. 4). The initial step involved redrawing

the Foerster dermatome map based on his original clinical photographs (Foerster, 1933; Bumke and Foerster, 1936) and that of Head and Campbell (1900) onto a figure outline. Both maps were then overlaid to delineate those dermatomal areas common to both—all remaining areas were deleted. This new template was then modified in the light of other good category evidence data for C6, C7, and C8 (Inouye and Buchthal, 1977) and L4, L5, and S1 (Cole et al., 1968; Nitta et al., 1993). The resultant map represents the most consistent tactile dermatomal areas for each spinal dorsal nerve root found in most individuals, based on the best available evidence. The evidence for the distribution of lumbosacral dermatomes is greater than that for cervical dermatomes. The dermatomal areas shown are not autonomous zones of cutaneous sensory innervation since, except in the midline where overlap is minimal, adjacent dermatomes overlap to a variable extent. Sherrington (1893, 1898) showed that the distribution of sensory nerve fibers is less

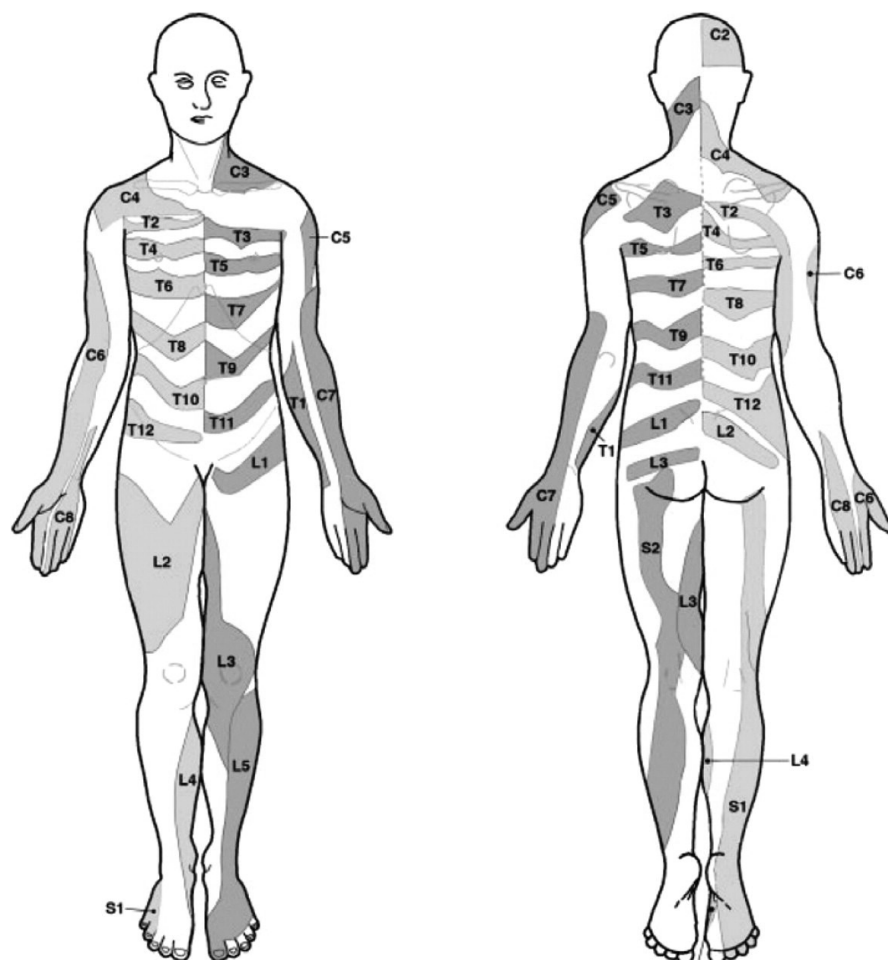
dense toward the periphery of a dermatome and thus the map probably reflects the areas of most intense cutaneous sensory innervation for that particular spinal nerve root.

A few further clarifications are necessary. In the upper limb, the C6 dermatome is based on Foerster (Foerster, 1933; Bumke and Foerster, 1936) because of the superiority of his isolation technique. C7 is based on relatively little evidence; Bumke and Foerster (1936) only determined the superior border of C7 and Head and Campbell (1900) were unable to verify the root levels for C6 and C7. Inouye and Buchthal (1977) reported substantial overlap of C6 and C7 in the thumb, as found in primates (Dykes and Terzis, 1981). C7 probably supplies the middle finger in many individuals, as suggested by Bumke and Foerster (1936) and demonstrated by Inouye and Buchthal (1977) but there is considerable overlap in this digit with C8 (Inouye and Buchthal, 1977). In a case report of a patient undergoing therapeutic sequential dorsal rhizotomy of T1, C8, and

**Table 2. The evidence base for human dermatome maps**

Method	References	Quality of evidence
Isolation of a single dorsal nerve root by surgical section of several (at least two) adjacent dorsal nerve roots above and below and mapping of residual area of cutaneous sensation in humans	Foerster (1933); Bumke and Foerster (1936)	Good
Division of several adjacent dorsal nerve roots above OR below the dermatome to define its proximal or distal boundary, respectively	Foerster (1933); Bumke and Foerster (1936)	
Recording of mixed spinal nerve sensory action potentials after electrical skin stimulation in humans	Inouye and Buchthal (1977)	
Distribution of skin erythema and blistering after herpes zoster reactivation (shingles) in humans together with histologic confirmation of dorsal root ganglion level	Head and Campbell (1900)	
Local anesthetic spinal nerve block and mapping of sensory impairment in humans	Poletti (1991); Nitta et al. (1993); Wolff et al. (2001)	
Distribution of cutaneous sensory impairment after intervertebral disc prolapse in humans	Falconer (1946); Keegan (1947); Keegan and Garrett (1948); Davis et al. (1952)	Intermediate
Sectioning of several nerve roots above and below isolated dorsal nerve root in macaque monkeys and mapping residual sensation	Sherrington (1893), (1898); Kirk and Denny-Brown (1970)	
Recordings of action potentials in single fibres of dorsal spinal nerve roots after cutaneous stimulation in primates	Dykes and Terzis (1981)	
Dermatome somatosensory evoked potentials recorded at nerve rootlets after electrical stimulation of skin in primates	Kuhn (1953)	
Complete sectioning of a specific spinal nerve	Cole et al. (1968)	
Electrical (Faradic) stimulation of distal part of an isolated and divided posterior nerve root and mapping of the resultant area of cutaneous vasodilatation in humans	Foerster (1933); Bumke and Foerster (1936)	
Electrical stimulation of mixed spinal nerves within intervertebral foramina and recording of pain and parasthesiae	Poletti (1991); Wolff et al. (2001); Slipman et al. (1998)	
Anatomical dissection in humans	Bolk (1898–99); Maigne et al. (1989)	
Topical strychnine poisoning of sensory pathways in humans and mapping of hyperesthesia	Klessens (1912)	Poor
Sensory loss after spinal cord injuries	Thorburn (1893); Starr (1892) and (1894)	
Evaluation of sympathetic dermatomes in man using electrical skin resistance mapping or cutaneous thermography	Richter and Woodruff (1945); Ash et al. (1986)	





**Fig. 4.** The evidence-based dermatome map representing the most consistent tactile dermatomal areas for each spinal dorsal nerve root found in most individuals, based on the best available evidence. The dermatomal areas shown are NOT autonomous zones of cutaneous sensory innervation since, except in the midline where overlap is minimal, adjacent dermatomes overlap to a large and variable extent. Blank regions indicate areas of major variability and overlap. S3, S4, and S5 supply the perineum but are not shown for reasons of clarity.

C7 roots, the cortical somatosensory evoked potential from stimulation of the middle finger was only abolished after section of the C7 dorsal root (Nemecek et al., 2003). In conclusion, C7 overlaps considerably with C6 and C8 and usually supplies the middle finger. C8 and T1 both supply the little finger (Inouye and Buchthal, 1977). This overlapping of cervical dermatomes in the hand is also supported by functional MRI studies of the cervical spinal cord (Stroman et al., 2002).

The dorsal distribution of T3–T12 is based solely on Head and Campbell (1900) who uniquely studied this distribution. The dorsal cutaneous surface of the hallux is most commonly innervated by L5 but can be supplied by L4 (Haymaker and Woodhall, 1953; Nitta et al., 1993). The S1 dermatome extends up the posterior aspect of the thigh probably as far as the buttock and overlaps with S2 (Cole et al., 1968; Nitta et al., 1993). Finally, it is generally agreed that C1 normally has no clinically detectable cutaneous sensory distribution (Haymaker and Woodhall, 1953; Poletti, 1991; Bonica and Loeser, 2001) and that S3, S4, and S5 supply the perineum including the anus and external genitalia (Bumke and

Foerster, 1936; Haymaker and Woodhall, 1953; Bonica and Loeser, 2001).

## Discussion

The aims of the present study were twofold: to undertake a systematic literature review of the available evidence for human dermatomes and, using the best available data, to construct a novel dermatome map.

It is all too apparent that current dermatome maps are inaccurate and there is a lack of consensus about the location and size of individual dermatomes. Although these schemata may be more aesthetic than our proposed map, they are less reliable, failing to highlight overlap, and individual variation. Dermatomes are much larger than shown in current anatomy texts. A less rigid approach to understanding dermatomes is required. We should not only highlight their orderly sequence, areas of consistency and clinical usefulness but also emphasize their overlap and variability. This we have attempted to do in our evidence-based dermatome map.

So why are dermatomes so variable? Almost all areas of skin are innervated by

two or more spinal roots. This accounts for some of the variability between individuals. Another reason for such variability may be due to the presence of intrathecal intersegmental anastomoses between dorsal spinal rootlets, enabling sensory neurones with a ganglion cell at one dorsal root ganglion to enter the spinal cord at a different level (Moriishi et al., 1989). In a study of 100 adult human cadavers intrathecal intersegmental anastomoses (spanning a maximum of one segment) were found in 61, 7, and 22% of cervical, thoracic, and lumbar dorsal roots, respectively. More individual variation might therefore be expected in upper limb dermatomes than elsewhere.

Kirk and Denny-Brown (1970) suggested that we reconsider the artificial concept of a dermatome as a discrete anatomical area. In the macaque monkey, they sectioned dorsal nerve roots intradurally or extradurally proximal to the dorsal root ganglia, or they divided both dorsal and ventral roots extradurally immediately distal to the dorsal root ganglia. In each case, three roots cranial and caudal to the isolated root were sectioned. The monkeys' sensitivity to pin scratch was examined daily for 2 weeks and then less often for a further 3 months. They found that the dermatomal area was greater if neighboring spinal nerves were sectioned distal to their dorsal root ganglia indicating some facilitatory action of neighboring intact ganglion cells or their central processes.

In a subsequent study, Denny-Brown et al. (1973) found that the dermatomal area increased if the spinal cord was sectioned just below the test segment (avoiding vascular infarction). The facilitatory and inhibitory effects of neighboring nerve roots and spinal segments, respectively was traced to the dorsolateral tract of Lissauer (which separates the tip of the dorsal horn from the surface of the cord). This area is now understood to exert facilitatory and inhibitory effects on synaptic transmission through the central synapses of the dorsal root sensory neurons. Thus, the dermatome distribution corresponding to a dorsal root ganglion is slightly different from that corresponding to a dorsal root and these areas in turn are influenced by spinal cord processing. Dermatomes not only vary according to their method of assessment and the type of sensation tested, but also precisely which neural element is being assessed (mixed spinal nerve, dorsal nerve root, spinal cord segment, etc).

## Conclusions

This systematic review of the literature demonstrates that current dermatome maps



are inaccurate. Using the best evidence currently available, a novel dermatome map was constructed representing the most consistent tactile dermatomal areas for each spinal dorsal nerve root found in most individuals. In addition to highlighting their orderly sequence and areas of consistency, features which are so useful in clinical practice, the evidence-based map displays large blank areas where overlap and variability are the rule.

Anatomy's status as a science has diminished in recent years (Dyer and Thorndike, 2000) and this underlines the need to apply rigorous methods to anatomical problems. This review demonstrates that an evidence-based approach to an anatomical concept is both justified and rewarding.

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# Commentary on “An evidence-based approach to human dermatomes”

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In this landmark article on human dermatomes, Lee et al.<sup>1</sup> give a fascinating account of how these were described using a total of 16 different methods dating back to 1900. Most of the classic anatomical texts present their own crisply delineated, almost sanitised, versions of dermatome maps based on the three early cardinal studies. Interestingly none of the maps highlights the concept of overlapping dermatomes, presumably because this might make the maps difficult to read. However, this concept is highly important clinically; the implication is that dermatomes are essentially twice as large as what we see on the maps. This is because almost every part of the skin is supplied by two spinal nerves and centrally there are considerable intersegmental anastomoses of dorsal spinal rootlets, especially for the upper limb nerve roots.<sup>2</sup>

This makes naming the level of spinal nerve root compression an educated guess at the best. I have certainly had some surprises clinically when I have sent off a patient for an MRI convinced that the level involved was S1, only to find it is L5, or vice versa. Sometimes other neurological signs such as reduced ankle jerk or muscle weakness add to the strength of conviction about a level.

Top of their list of quality evidence are the ethically dubious studies by Foerster and Bumke<sup>3,4</sup> sectioning spinal nerve roots to relieve spasticity in Nazi Germany. They noted that tactile dermatomes are larger than those determined by pain and temperature sensation. They also claimed that, with the exception of C2, there is no clinical sensory loss if only one nerve root is sectioned, although this was later disputed by Keegan and Garrett<sup>5</sup> who found that hypoaesthesia with single nerve root compression is

28% of cervical disc prolapses and 56% of lumbar disc prolapses. This finding encourages us to consider that more than one nerve root may be compressed in a large proportion of patients with radicular pain and paraesthesia.

In the elegant work of Head and Campbell herpes zoster eruptions in over 400 patients were used to map the dermatomes.<sup>6</sup> Unlike Foerster and Bumke, they were able to describe all 12 thoracic dermatomes. However, the accuracy of their work was challenged by the recognition by Lewis in 1958 that herpetic eruptions may affect several adjacent dorsal ganglia.<sup>7</sup> This explains why the rash of shingles may spread over several adjacent dermatomes. Conversely, a rare presentation of shingles called “zoster sine eruption” or “zoster sine herpette” has been described where there is no skin eruption following the prodromal pain. The diagnosis may be supported by demonstrating a rise in IgM and eventually IgG varicella antibody titres.<sup>7,8</sup>

Keegan and Garrett's work based on patients with disc prolapses causing nerve root compression added to the previous work but only for dermatomes involving the limbs.<sup>5</sup> Their work was the most methodologically unsound of the three studies. Certainly their depictions of sensory loss from disc prolapses extending proximally to the spinal midline do not match with a subsequent study by Davis et al.,<sup>9</sup> nor do they match with any patient I have ever seen. They represent generous extrapolations of patterns of distal sensory loss.

The authors use most of the 16 methods to define dermatomes to synthesise their own “evidence-based” dermatome map. This approach results in rather irregular

outlines for most dermatomes – certainly not as easy to commit to memory and not as tidy as a conventional dermatome map, but something that serves as a useful reference on the desktop or the wall above the consulting desk. In common with other maps, we need to keep in mind, however, that it still tells only half of the dermatome story – the remainder of each dermatome lurks on either side of the central strip shown. Nonetheless it probably offers the most accurate account of the dominant dermatomes on any given part of the skin and so acts as the best reference for clinicians interested in accurate diagnosis of conditions that manifest in a dermatomal distribution.

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# Joint hypermobility and motor control

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## Introduction

There are no precise prevalence rates of adults with generalised joint hypermobility (GJH), and in a recent review the prevalence for adults varies from 2% to 57% depending on age, gender and ethnic origin.<sup>1</sup> For children the prevalence varies from 7% to 36%, primarily depending on the tests and criteria (especially the cut-off points) used for diagnosing GJH.<sup>2,3,4,5</sup>

Hypermobility presented as GJH alone and in combination with certain symptoms (e.g. hypermobility syndrome, Ehlers-Danlos syndrome) are described in combination with neuromuscular and

functional deficits seen in adults. Common rehabilitation strategies for this condition are also discussed here.

Joint mobility is a continuous trait that varies with joint location and is strongly influenced by age, gender, and ethnic origin.<sup>1</sup> No matter the type of mobility (hypo-, normo- or hypermobility), we anticipate that variation in mobility begins in utero as part of the individual's phenotype.

Joint hypermobility (JH) has been known for centuries, but not until the last 50 years has it gained a more profound and increasing scientific interest. The reason for that is probably an often observed concomitant

presence of JH and musculoskeletal pain, giving rise to the name hypermobility syndrome (HMS).<sup>6</sup> The name was later redefined by an interest group of the British Society of Rheumatology as benign joint hypermobility syndrome (BJHS), which included more signs than just musculoskeletal complaints<sup>7</sup> (Table 1).

However, hypermobility and pain are also part of the Villefranche criteria for the various types of Ehlers-Danlos syndromes (EDS),<sup>8</sup> as well as the criteria for Marfan syndrome, osteogenesis imperfecta, and other diseases belonging to the group of hereditary disorders of connective tissue (HDCT).

*Table 1. Review of hypermobility syndrome definitions*

Publication	Tests and Clinical Signs		Syndrome criterion
Kirk JA, et al 1967	Carter & Wilkinson's tests with > 3 positive joint pairs. Musculoskeletal complaints (without any other systemic rheumatic disease)		None
Grahame R, et al 2000	Major criteria	Minor criteria	BJHS is diagnosed in the presence of: 2 major criteria OR 1 major and 2 minor criteria OR 4 minor criteria
	1.Beighton score $\geq 4/9$ (either currently or historically) 2.Arthralgia for longer than 3 months in 4 or more joints	1. Beighton score of 1, 2, or 3/9 (0 - 3 if age 50+) 2. Arthralgia $\geq 3$ mo in 1–3 joints, or back pain $\geq 3$ months or spondylosis, spondylolysis/spondylolisthesis 3. Dislocation/subluxation in more than one joint or in one joint on more than one occasion 4. Soft tissue rheumatism $\geq 3$ lesions (e.g., epicondylitis, tenosynovitis, bursitis) 5. Marfanoid habitus (tall, slim, span/height) ratio > 1.03, upper/lower segment ratio < 0.89, arachnodactyli (+ Steinberg/wrist signs) 6. Abnormal skin: striae or hyperextensibility, thin cutis or papyraceous scarring 7. Eye signs: drooping eyelids or myopia or antimongoloid slant 8. Varicose veins or hernia or uterine/rectal prolapse	2 minor criteria will suffice where there is an unequivocally affected first degree relative
			BJHS is excluded by presence of Marfan or EDS (other than the EDS hypermobility type)
			Criteria major 1 and minor 1 are mutually exclusive, as are major 2 and minor 2



Clinical characteristics

Normal/abnormal joint movement

According to the American Academy of Orthopedic Surgeons (AAOS)<sup>9</sup> it is not possible to precisely determine mean joint mobility throughout the body. Consequently, the AAOS developed consensus-based estimates in degrees derived from statistical means based on reports from four committees of experts.

In general, joint mobility is regarded as a graded phenomenon,<sup>10</sup> and a consensus has developed that individual joint mobility follows a Gaussian distribution.<sup>11,12,13</sup> With this in mind, abnormal joint mobility would reflect movements that deviate from the mean with  $\pm 2$  standard deviations (SD), i.e. the general consensus-based estimates. However, for practical purposes range of motion (ROM) measurements in degrees are not manageable when testing for generalized JH (GJH). Instead, the Beighton tests that apply a dichotomous principle are widely used,<sup>14</sup> even though the Rotès-Quérol tests<sup>15</sup> are used more in Spanish- and French-speaking countries. The Beighton tests were described about 40 years ago,<sup>16</sup> but only by photos and short legends to figures (Figure 1).

The description was repeated a few years later with minor changes in the photographic presentation.<sup>14</sup> However, since then there has been a considerable variation in the descriptions in the literature on how to perform the various tests, but also in the cut-off level for a positive test and in the definition of GJH (Table 2).

The Beighton tests as well as the criteria for GJH have high inter-examiner reproducibility in children<sup>17</sup> as well as

in adults,<sup>18,19</sup> and so have the Rotès-Quérol tests.<sup>18</sup> The concurrent validity also seems to be high, as a positive Beighton test equals normal mean ROM + 3 SD<sup>12</sup> and as GJH has high correlation to a global joint index.<sup>18</sup> The predictive value of GJH has been tested only in school populations aged 10-14 years. The studies showed that 10-year old children with GJH and musculoskeletal pain had an increased risk of still having this pain at 14 years of age.<sup>3,20</sup> However, 10-year-old children with GJH and no musculoskeletal pain did not have increased risk of developing musculoskeletal pain at 14 years.<sup>21</sup> A recent study found that GJH at 13.8 years was a risk factor for pain at 17.8 years in the shoulder, knee and ankle/foot with the greatest mechanical forces. However, the study did not describe whether pain was present in those with GJH already at 13.8 years of age.

**Hypermobility syndrome versus EDS, hypermobile type**

The criteria for these two syndromes – the Villefranche criteria<sup>8</sup> and the Brighton criteria<sup>7</sup> – are in essence proposals or recommendations for a classification of two different disease entities. However,

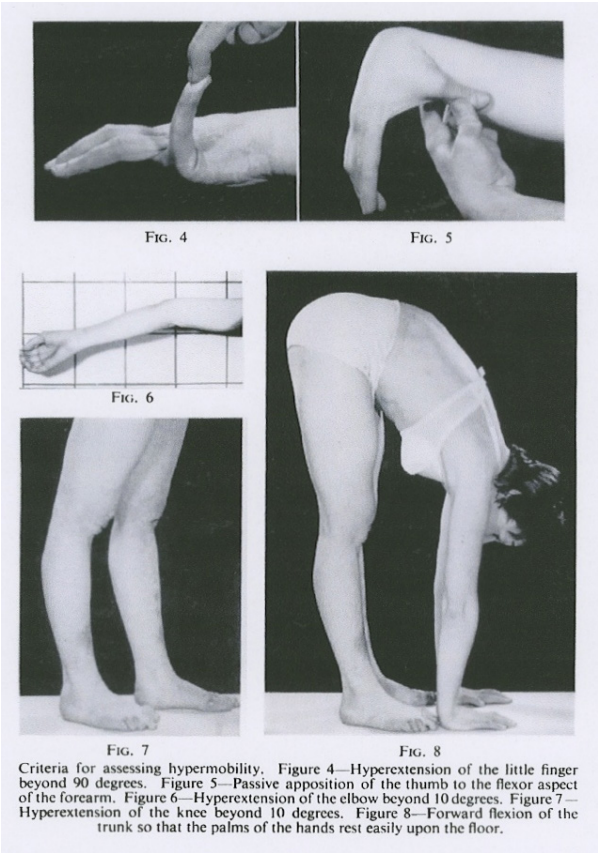


Figure 1. The original presentation of the hypermobility tests.

there is a considerable overlap in the most important criteria items suggested (Table 3).

The inter-examiner reproducibility of diagnosing BJHS by the Brighton criteria is high.<sup>19</sup> However, the reproducibility for diagnosing the various EDS entities has never been published, nor has the validity of the criteria sets and – very important for the clinician – the predictive value of a positive and a negative test result.

The overlap in the criteria was already known by the authors when they presented the Brighton criteria: “From the clinic perspective there is compelling evidence

Table 2. Examples of various definitions of GJH, given as number of positive tests in proportion to applied tests.

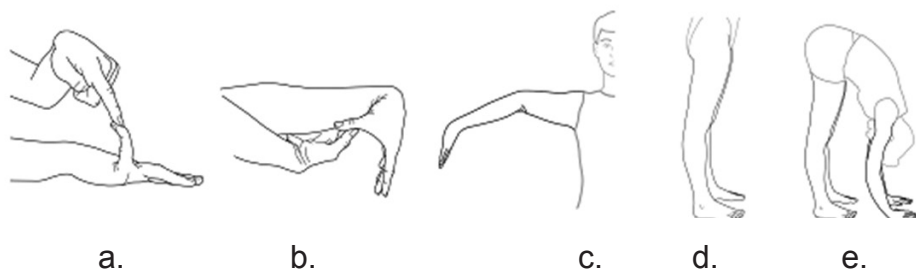
Method	Tests	Definition	Comment
Rotès-Quérol, 1957	3 tests	2/3	Adults
Carter & Wilkinson, 1964	C&W tests	$\geq 3/5$	Children, 6-11 year
Beighton (5 tests), 1969	Beighton tests	None	Adults
Rotès-Quérol, 1972	R-Q tetss	None	Degré I - IV
Beighton (9 tests), 1973	Beighton tests	None	TwsanaAfricans
Hospital del Mar Criteria, 1992	Del Mar tests	4-5/10	Gender dependent
Mikkelsen et al. 1996	Beighton tests	$\geq 6/9$	Children
Villefranche criteria, 1998	Beighton tests	$\geq 5/9$	Age, gender, ethnicity
Brighton criteria, 2000	Beighton tests	$\geq 4/9$	Current or historical

Table 3. Comparison of important items in the Villefranche criteria for Ehlers-Danlos syndrome (EDS) and the Brighton criteria for Benign Joint Hypermobility Syndrome (BJHS).

	EDS classical type	EDS hypermobile type	Benign joint hypermobility syndrome
Major criteria	Skin hyperextensibility	Hyperextensible and/or smooth velvety skin	
	Widened atrophic scars		Arthralgia for longer than 3 months
	Beighton score $\geq 5/9$	Beighton score $\geq 5/9$	Beighton score $\geq 4/9$
Minor criteria	Smooth, velvety skin	Chronic joint/limb pain	Skin hyperextensibility, or papyraceous scarring
	Dislocations/subluxations	Recurring joint dislocations	Dislocation/subluxation
	Positive family history	Positive family history	Positive family history*

\* Not a criterion item per se





- a. With patient seated, ask her/him to place the forearm and hand, pronated on the table and ask the patient to extend passively the 5th finger. An extension beyond 90° indicates a positive test.
- b. With patient seated, arm flexed 90° in shoulder, elbow extended 180° and hand pronated and relaxed, ask the patient to move passively the first finger to the volar aspect of the forearm. In case the forearm is reached the test is positive.
- c. With patient standing in front of you, ask her/him to abduct 90° in the shoulder with relaxed elbow and supinated hand. Support the upper arm with your ipsilateral hand. An extension beyond 10° indicates a positive test.
- d. With patient standing in upright position, turning the side towards you, ask her/him to relax and hyperextend the knee. An extension beyond 10° indicates a positive test.
- e. From standing position, with her/his feet slightly apart, ask the patient to place his hands on the floor maintaining extended knees. In case the palms of the hands easily can be placed on the floor, the test is positive.

Tests a. to d. are double-sided, giving in total nine tests.

**Figure 2.** Test performance and description of Beighton tests shown to be reproducible.

that the hypermobility type of EDS and the BJHS are one and the same",<sup>7</sup> and recently it was recommended the two disease entities be merged into one.<sup>23</sup> However, research in the last 10 years should be taken into account in a revision of the syndrome criteria.<sup>24</sup>

## Alterations in motor control in subjects with GJH

In adults, it is generally important to distinguish between non-symptomatic GJH and symptomatic GJH (such as HMS, EDS-HT). Adults with GJH do not necessarily have other problems (for example, pain or reduced function) other than the fact that they are more flexible than their contemporaries. Children and adolescents seem to perform better than their peers, since they have better balance,<sup>4</sup> are better in precision tasks,<sup>5</sup> jump higher,<sup>5,25</sup> and are often selected into elite sports, dance and music playing, partly due to their greater flexibility.<sup>26,27</sup> However, that does not quite seem to be the same for the adults. Actually their stability is reduced.<sup>28,29,25</sup> Whether this is due to decreased flexibility with ageing is not known. However, it indicates that this condition deteriorates with age.

It is not known when and who will develop pain and reduced function. But since GJH and pain in 10-year-old children is a predictor of repeated non-specific pain and pain in the lower extremities four

years later,<sup>3,20</sup> it indicates that when pain has emerged in childhood, it seems to stay.

Adults with symptomatic GJH, called hypermobility syndrome (HMS), are typically seen in the healthcare system, in contrast to adults with non-symptomatic GJH. Pain in HMS may emerge either directly as diffuse and/or joint pain or indirectly due to mechanical trauma (dislocation, luxation). Since an increased risk of luxation, especially in contact sports, has been found in children as well as in adults with GJH,<sup>30</sup> pain in HMS may very often be a consequence of smaller or larger injuries. The body region most often involved is the knee,<sup>30,31</sup> but the shoulder may also be involved.<sup>32</sup>

## Maximal strength and strength balance

Adults with HMS or EDS-HT<sup>33,34</sup> have decreased maximal strength in isokinetic strength of knee extension, and those with EDS-HT also have reduced endurance.<sup>34</sup> It is well known that pain is an important inhibitor in maximum voluntary muscle contraction, such as seen in osteoarthritis (OA)<sup>35</sup> and in experimental pain,<sup>36</sup> hence reduced strength in HMS and EDS-HT could be due to pain. The reason for reduced strength in EDS-HT has also been ascribed to severe neuromuscular involvements.<sup>37,38</sup>

Reduced knee strength may also be due to hypermobility alone, as seen in a recent study where women (and also girls at 10 years of age) with non-symptomatic GJH

had significantly lower maximum isokinetic knee extension strength than their matched contemporaries without GJH.<sup>25</sup> When tested isometrically though, there was no strength difference.<sup>28,29</sup> This means that in the total group (men and women together), adults with GJH do not have reduced maximal strength, neither isokinetically nor isometrically, compared with a matched control group without GJH. However, since adults with GJH have an increased risk of injuries, a normal maximal strength does not seem to protect against injury. Knee strength balance, called hamstring/quadriceps-ratio (H/Q-ratio), previously reported to be an important predictor of ligament and muscle injuries,<sup>39</sup> may be a more important protecting factor. The H/Q-ratio was actually reduced in adults with HMS and GJH<sup>33,25</sup> when measured isokinetically. Also decreased knee muscle activity balance was seen in adults with GJH during maximum isometric knee extension.<sup>29</sup> These different signs of strength and muscle activity imbalance in GJH could result in the increased risk of injuries (like in GJH), and this may result not only in pain but also in increased risk of OA over time.<sup>40</sup>

Several automatic protective motor control strategies for joint stabilisation seem to be present in adults with non-symptomatic GJH. This was found as an increased co-contraction level (muscle activity in both agonists and antagonists of the knee) during submaximal knee extension, correlating positively with the Beighton score, and in normal balance tasks.<sup>41,42,29</sup> Further, an increased ability to develop explosive muscle force (rate of force development) during maximum knee extension was seen in women with non-symptomatic GJH, as another protective strategy due to reduced stability in the passive structures.<sup>28</sup>

## Proprioception

Joint instability in patients with EDS-HT could be related to the poorer proprioception as found in adults with EDS-HT and with HMS.<sup>43,44,45</sup> Disturbed sensory feedback mechanisms in subjects with HMS were further confirmed in adolescents where the reflex in the knee extensors was absent in 47% of 15 patients, compared to none in the healthy controls.<sup>46</sup> However, poor reflexes may be due to the presence of pain, since non-symptomatic adults with GJH seemed to have normal sensory feedback mechanisms (seen as normal proprioception) compared to healthy controls.<sup>47</sup> Further research is needed in

this area.

Proprioception acuity may be improved with training, but only a few studies on HMS have shown this.<sup>48,44</sup>

## Gait

An increased knee joint moment in the sagittal (extensor) and frontal planes (abductor), 10% and 13%, respectively, was seen in adults with GJH.<sup>49</sup> Previous studies have estimated at least 1% increase in knee abduction moment to increase the risk of OA progression 6.46 times in patients with OA.<sup>50,51,52</sup> Also adults with EDS-HT walked with significantly decreased step velocity, step length and stride length.<sup>53</sup>

## Balance

A larger sway in static balance as seen in non-symptomatic women with GJH could be due to poorer ability in active stabilization in the frontal plane, where balance is more dependent on passive stabilization.<sup>28</sup> In dynamic and thus more challenging balance conditions non-symptomatic adults with GJH showed less stable trunk segments and less lateral shoulder stability, indicating a less flexible moving pattern. This may compensate for an increased risk of falling.<sup>54</sup> In adults with EDS-HT whole body stability or postural control is diminished, and they further reported fear of falling and also had an increased risk of falling, since 95% of these patients fell in the previous year.<sup>53</sup> These results indicate a threat to safety during everyday situations for this patient group.

## Physical fitness (endurance)

Adults with HMS and EDS-HT have reduced endurance (in maximum repetitions of knee extension and flexion at 240°/s).<sup>33,34</sup> Also, the static endurance test showed that the EDS-HT patients were fatigued twice as fast as controls in the time to maintain a specific posture.<sup>34</sup>

# Rehabilitation in GJH and HMS

## General principles

In general, knowledge and perception of the problems that may arise from GJH and HMS are essential. Tailored care in terms of evidence-based diagnostic procedures and clinical expertise is essential in order to construct classification models as well

as optimized treatment strategies. So diagnostics and treatment should be founded on evidence-based practice, clinometric and clinical reasoning, eventually leading to sub-classification and treatment strategies.

This requires a shared language, as well as a common framework. In this context, a framework that could be used as the classification for health and health-related domains is the International Classification of Functioning, Disability and Health,<sup>55</sup> known more commonly as the ICF model. The ICF domains are classified from bodily, individual and societal perspectives by means of two levels: the level of body functions and structure and the level of activity and participation. Since an individual's functioning and disability occur in a context, the ICF also includes a list of environmental factors.

Although the ICF is frequently used in the provision of healthcare services, it has not been described in detail in adults with GJH, HMS and EDS-HT.

Intervention, based on clinical decision making, might be effective using the principles of motor learning and training. Reassurance, education and joint care are cornerstones of treatment strategies.<sup>56</sup> For this, a multidisciplinary approach might be indicated, depending on the problems an individual patient will encounter. Treatment has to be tailored to the individual's needs, and where patients encounter problems on more than one domain (psychological, physical and social), the recommended treatment is multidisciplinary.<sup>57</sup>

The motor learning principles as described in a textbook: 1) Use it or lose it, 2) Use it and improve it, 3) Specificity, 4) Repetition, 5) Intensity, 6) Time, 7) Salience, 8) Age, 9) Transference, and 10) Interference<sup>58</sup> should be expected to achieve physiological change over time. Also interventions, which should take into account transfer and generalization, need attention. A standardized program should enhance the transference and generalization of a task, indicating that tasks or exercises are given in a random order. This also indicates that variation of practices should be performed, meaning that specific tasks or exercises are performed in different contexts.

Treatment strategies should focus on influencing the pathophysiological aspects of GJH and HMS combined with the goals for activities and participation of the individual patient. Although the amount of joint hypermobility cannot be influenced, improving musculoskeletal strength, stability and coordination, as well as physical fitness should be based on pathophysiological principles.

In general, cardiovascular training and strength training are both important categories of physical fitness. Guidelines for cardiovascular and strength training for adults are very well described by the American College of Sports Medicine (ACSM).<sup>59</sup> A program of regular exercise that includes cardiorespiratory, resistance, and neuro-motor exercise training, beyond activities of daily living to improve and maintain physical fitness and health, is essential for most adults. The recommended minimal frequency of aerobic training for adults is 3-5 times a week, with duration of 30-60 minutes of purposeful moderate exercise. The recommended volume for a training session is a minimum of 500-1000 metabolic equivalent minutes per week or a minimum of 2000-7000 step counts per day.

Muscular fitness and its relationship to health has been well established during the past decade.<sup>60</sup> The recommended frequency for training of muscle strength is 2-3 times a week for each muscle group. The intensity is based on 60-70% of one Repetition Maximum (RM) (moderate to hard intensity) for novice to intermediate exercisers in order to improve muscle strength.

Neuro-motor exercise training incorporates motor skills such as balance, coordination, gait, and agility, and proprioceptive training. Neuro-motor exercise training is beneficial as part of a comprehensive exercise program, especially to improve balance, agility, muscle strength, and to reduce the risk of falls.

## Randomized controlled trials

A literature search was performed (Pubmed, Cinahl) to find randomized controlled trials focusing on interventions on GJH and HMS in children and adults.<sup>57</sup> Only one randomized controlled study was found on adults, studying knee proprioception and effects of proprioception exercise in adolescent and adult patients with benign joint hypermobility syndrome. To evaluate the proprioceptive sensibility of the knee joint, cases with HMS were randomized into two groups: proprioceptive exercises were undertaken by 15 patients for 8 weeks, and 25 patients were taken as controls and did not receive any treatment. In the HMS group, significant decreases in pain levels were detected in individuals who did exercises compared with those who did not, and also statistically significant improvements were detected in occupational activity for those who engaged in exercise. However, no between-group differences were reported, only within-group differences.<sup>44</sup> Two

uncontrolled studies have further been published in adults. Appropriate exercises led not only to symptomatic improvement, but also to demonstrable enhancement of proprioception, although both studies lacked a control group.<sup>61,48</sup>

In children, three randomized controlled trials were found.<sup>56</sup> One study performed a prospective randomized controlled trial (RCT), comparing a six-week generalized program, including muscular strength and fitness training, with a targeted program aiming at correcting motor control of symptomatic joints. Fifty-seven children, aged 7-16 years with symptomatic GJH, were randomly assigned to receive a targeted or generalized training program. The study demonstrated significant and sustained reduction of pain and improved self-reported function when the effects of both groups were combined, but did not detect any difference between the groups.<sup>62</sup>

One study of infants on delayed motor development caused by joint hypermobility and benign hypotonia examined the effect of the frequency of physical therapy.<sup>63</sup> The study groups comprised 29 infants (8-12 months) who were randomly placed into a monthly or weekly treatment group. No difference in self-reported (by parents or their children) and measured function was found between the two study group scores on the different tests at all assessment points. However, one exception was the assessment of walking at the age of 15 months, which revealed a clear advantage for the infants who were treated weekly.

In children and adults, further uncontrolled studies or therapeutic strategies have been described in textbooks.<sup>64,65</sup> The recent topical review reported that joint protection and injury prevention form a major component of a successful rehabilitation program.<sup>65</sup> These aims are achieved through improving posture, joint stability and specific motor-skills by including pain-free exercises to enhance proprioception and muscle strength. Also, renewed confidence in the joints leads to resumption of a person's habitual level of physical activity, with additional benefits of improved physical fitness and wellbeing. In addition, the review questioned the optimal form of rehabilitation to maintain joint health in HMS.<sup>65</sup>

Unfortunately, until now, physiotherapy treatment techniques with demonstrated effectiveness are scarce in HMS. Since observations are primarily based on uncontrolled trials, there is a need to be cautious about interpretations of the literature.

As mentioned in the review of joint protection and rehabilitation in the adult

with hypermobility syndrome, it is not yet known which is the optimal physical rehabilitation program. As long as scientific evidence of optimal treatment is lacking (evidence-based), recommendations can be made only "best opinion" (practice-based).<sup>65</sup> Physiological training principles used in healthy persons should be used in the care of patients with HMS, since overuse and triggering musculoskeletal complaints have been reported. Therefore: train as effective as possible based on clinical reasoning and evidence-based practice/practice-based evidence, but handle with care!

In summary, generalized joint hypermobility is a condition which, when present with symptoms, is characterized by decreased muscle strength, stability and proprioception, in addition to impaired gait pattern, balance and physical fitness such as endurance. Treatment evidence is lacking. However, although the amount of joint hypermobility cannot be influenced, improving musculoskeletal strength, stability and coordination, as well as physical fitness is the aim, and should be based on pathophysiological principles.

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# How effective is glucosamine in the treatment of osteoarthritis compared to placebo and chondroitin? A review of the best evidence

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## Introduction

Osteoarthritis (OA) is the most common form of arthritis and is a source of chronic pain, disability and decreased quality of life for many people, particularly adults over 50.<sup>1,2</sup> It affects more than 1.3 million Australians and affects females to males in a 3 to 1 ratio.<sup>1,2</sup> Management of OA is a challenge for health care professionals. There are a wide range of management options that have varying levels of evidence for their efficacy. These include exercise, ambulatory aids, weight loss, pharmaceuticals, surgery, intra-articular injections and complementary medicines (CAM). In 2004-5, the Australian Bureau of Statistics National Health Survey (ABS NHS) established that 40% of Australians with OA use pharmaceuticals and 46% use dietary supplements.<sup>1</sup> One of the most common supplements taken in Australia is glucosamine. It is also available in a combination tablet with chondroitin. Twenty six per cent of females and 21% of males with OA in the ABS NHS reported taking glucosamine.<sup>1</sup>

## Mechanism of action of glucosamine and chondroitin

Glucosamine comes in two forms: glucosaminesulphate (GS) and glucosamine hydrochloride (GH). GS and chondroitin sulphate (CS) are building blocks of the important components of articular cartilage called proteoglycans.<sup>3,4</sup> The predominant proteoglycan present in articular cartilage is aggrecan, which is rich in chondroitin sulphate.<sup>5</sup> Aggrecan has osmotic properties which help combat the compressive loads placed on the articular cartilage between joints.<sup>5,6</sup> It is proposed that glucosamine

is a substrate for the biosynthesis of proteoglycans and glycosaminoglycans (GAGs).<sup>7</sup> Glucosamine is synthesized by chondrocytes from glucose to produce GAGs and this in turn stimulates proteoglycan production.<sup>7</sup> The rationale for use of glucosamine in OA is based mostly on animal and in-vitro models where promising results were seen, including a rebuilding of experimentally damaged cartilage, normalisation of cartilage metabolism and some anti-inflammatory effect.<sup>3,8</sup> It has been suggested that some of the dose of oral chondroitin and glucosamine (tablets or powder) reach the joint as both complementary and alternative medicines (CAMs) are partially absorbed in the intestine.<sup>6</sup> The recommended doses are: 1500-2000 mg daily for GS, and 800-1200 mg daily for CS.<sup>8</sup> Some research suggests that glucosamine and chondroitin have a slow onset of action and patients may not see improvements in symptoms for 6-8 weeks from when they start taking either CAM. The authors also stated that there could be a carryover effect, with relief of symptoms persisting two months after discontinuing the supplement.<sup>9</sup> Richy et al. stated that minimum time reported for the onset of a significant action was two weeks for both glucosamine and chondroitin; however the authors excluded trials with a treatment period of less than four weeks.<sup>4</sup>

There is considerable controversy regarding the analgesic and disease modifying efficacy of glucosamine in OA.<sup>3,10</sup> This uncertainty trickles down to a consumer level. Data from three national and one state-wide pharmacist-operated medicines call centres, indicate that many consumers were asking questions about glucosamine, including questions surrounding its efficacy.<sup>11</sup>

To address this uncertainty the question, "What is the efficacy of glucosamine in treating osteoarthritis in adults, compared

to placebo and chondroitin?" was posed to inform a literature search for reviews on this question. The databases used were Cochrane Library, Medline and Pubmed. This yielded 13 relevant reviews. Ten of these were not analysed because the reviews had a publication date before 2003,<sup>12-15</sup> reported a limited number of outcomes,<sup>16</sup> included a small number of participants,<sup>17,18</sup> or number of studies<sup>19,20</sup> contained results of low quality studies and did not focus on the question at hand.<sup>21</sup> This left three recent systematic reviews for critical appraisal.

## Critical appraisal of Cochrane review by Towheed et al.

This Cochrane review, of which the latest version was published in 2009, investigated the effectiveness and toxicity of glucosamine in OA.<sup>3</sup> Their literature search was extensive and included studies published by January 2008, with no language or age restrictions set.

Their inclusion criteria were outlined and included randomised controlled trials (RCTs) of OA at any site, excluding temporo-mandibular joint (TMJ) disorders.<sup>3</sup> This Cochrane review allowed RCTs that administered glucosamine by any route. All of the 25 RCTs included were double blinded. They utilised the GRADE criteria to critique the RCTs and assess whether the design and quality of RCTs was sufficient for inclusion in the review. The mean trial duration was almost six months (25.5 weeks) and the mean number of participants randomised in each of the 25 randomised parallel-group trials was 198, with a total of 4963 participants being captured in this review.<sup>3</sup> Most of the studies (80%) investigated OA of the knee exclusively.

A strength of the systematic review was

that it presented results both collectively (data from all 25 RCTs) and exclusively; using only data from higher-quality studies in which an appropriate method of allocation concealment had been described by the authors of the RCT. Just over half of the studies were rated as having adequate allocation concealment (13 RCTs, 52%).<sup>3</sup> Twelve of these 13 RCTs were included in a post-hoc sensitivity analysis. The reviewers decided that the remaining 48% had either insufficient or unclear concealment of allocation. One high-quality review was excluded due to a unique comparator.<sup>3</sup>

The particular product or brand used in the RCTs may impact on results and therefore may be a confounding factor. It has been postulated by some researchers that glucosamine hydrochloride is ineffective, whereas GS has shown more promising results.<sup>10</sup> Therefore it may have been useful if the results of this Cochrane review by Towheed et al. also presented the data regarding GS and GH analysed separately. Of the 12 studies included in the sensitivity analysis, seven exclusively investigated GS, whereas the other five investigated GS or GH supplementation.

This review also included a comparison of Rotta brand versus non-Rotta brand glucosamine. This can be viewed as both a strength and weakness of the systematic review. The inclusion of this comparison is advantageous because RottaPharm is an Italian manufacturer and in Italy and throughout the rest of Europe, glucosamine is considered a pharmaceutical and therefore is more highly regulated, in comparison to countries such as North America and Australia.<sup>3</sup> In these countries it is not classed as a pharmaceutical and is instead seen as a complementary medicine or dietary supplement. In Australia, glucosamine undergoes basic quality and safety assessments.<sup>22</sup> However there is no evaluation of efficacy or bioavailability of any of the glucosamine products available for consumer purchase.<sup>8</sup> A Canadian study by Russell et al. (discussed by Towheed) found that the actual dosage (in mg) of GS varied from 59% to 138% of the dose stated on the label.<sup>3,23</sup> This variability in dose could alone account for the heterogeneity amongst studies of the efficacy of glucosamine.

The positive results of GS, limited to the Rotta brand, raises questions about affiliations with the manufacturer, as 56% of the RCTs had some form of affiliation with RottaPharm (by evaluating Rotta brand or other relationship).<sup>3</sup>

There is evidence that research funded by pharmaceutical companies is more likely to have results favouring the sponsor, when compared to research with

funding from other sources.<sup>24</sup> This positive publication bias may be due to the failure of pharmaceutical companies to publish negative results and may have been a factor in this review.<sup>24</sup> However there is no evidence that the studies funded by pharmaceutical companies were of lower quality than those funded from other sources.<sup>24</sup>

## Results of Cochrane review by Towheed et al.

Of the 25 studies that met the inclusion criteria (including low quality and older studies), 18 studies were pooled for the outcome variable of reduction of pain. Towheed et al. found that glucosamine (GS or GH) improved pain more than placebo and this result was statistically significant (summary SMD [standardised mean difference] -0.47; 95% CI -0.72 to -0.23). The authors concluded that this corresponded to a 22% improvement in pain from baseline. Towheed et al. did note that there was variability amongst the results and there was not a positive consensus regarding glucosamine among all of the RCTs.<sup>3</sup> Towheed et al. also analysed 11 high-quality studies exclusively and concluded that there was no statistically significant difference in reported pain by participants compared to placebo. These patients were assigned to at least six months of treatment with glucosamine (GS or GH) at 1500 mg daily.<sup>3</sup> The summary SMD (random-effects model) was -0.16 (95% CI -0.36 to 0.04).<sup>3</sup>

The Lequesne Index was another outcome that was analysed by Towheed and fellow researchers. Lequesne Index score was developed by Lequesne et al. and has been used since 1987 to evaluate the effectiveness of therapeutic interventions regarding OA.<sup>25</sup> It is a questionnaire regarding pain or discomfort, maximum distance walked and activities of daily living.<sup>25</sup> For this outcome, Towheed et al. found similar results from pooling all of the data (five RCTs) and data from the sensitivity analysis for adequate allocation and concealment (four RCTs). For the five RCTs, Towheed et al. found that glucosamine was significantly superior to placebo in terms of its ability to improve Lequesne index scores. The summary SMD (random-effects model) was -0.47 (95% CI -0.82 to -0.12).<sup>3</sup> For the sensitivity analysis, the summary SMD was -0.54 (95% CI -0.96 to -0.12).<sup>3</sup> The authors noted that a negative SMD in these cases was indicative of a positive effect of glucosamine. Towheed et al. concluded that the results from the sensitivity analysis regarding Lequesne

Index corresponded to an 11% improvement in function from baseline. Many other outcomes were analysed by this Cochrane review and WOMAC pain, function and stiffness outcomes did not reach statistical significance.<sup>3</sup>

A total of 14 (56%) of the RCTs used Rotta brand GS as the only preparation that was used. A subgroup analysis of Rotta preparation was performed by Towheed et al. and a statistically significant benefit for GS over placebo was found for four outcomes: reduction in pain, Lequesne Index and WOMAC pain and function subscale scores. These results were based on different numbers of RCTs, being eight, five, seven and six respectively. The summary SMD value for reduction in pain was -1.11 (95% CI -1.66 to -0.57) and for Lequesne index this value was -0.47 (95% CI -0.82 to -0.12).<sup>3</sup> A negative SMD for these outcomes corresponded to glucosamine being significantly superior to placebo. This subgroup analysis, which reported positive effects of glucosamine compared to placebo, was derived from data of both high and low quality RCTs, and most of the RCTs solely investigated OA of the knee (62.5%) and the remainder either didn't specify site (25%) or studied multiples sites (12.5%).

Towheed et al. also reported on joint space narrowing (JSN) based on the results from two RCTs. Towheed et al. found the summary mean difference measuring minimum joint space width for the knee or hip was 0.32 (95% CI 0.05 to 0.58) after administration of 1500 mg daily for three consecutive years.<sup>3</sup> The authors state this is statistically significant in favour of glucosamine and therefore glucosamine may have an effect on the radiological progression of OA.

## Critical appraisal of meta-analysis by Richy et al.

A comprehensive meta-analysis published by Richy et al. in 2003 investigated the structural and symptomatic efficacy of glucosamine and chondroitin in knee OA.<sup>4</sup> Their extensive literature search included publication dates from 1980 to March 2002, with no limitations on language or age group and the two independent reviewers were blinded to sources and authors.<sup>4</sup> Their inclusion criteria were reasonable; however their minimum time frame was set at four weeks. This is a short time frame for a treatment intervention. This meta-analysis included only studies



where the administration was oral.<sup>4</sup> This is more relevant to the question at hand and differs from the Cochrane review by Towheed et al., which allowed RCTs where the administration of glucosamine was oral, intravenous, intra-articular, intramuscular or multiple routes. However it is important to note that in the review by Towheed et al., 72% (21 of 29 studies before final exclusion) were exclusively oral administration.<sup>3</sup> The review by Richy and fellow researchers analysed 15 studies with a total of 1775 patients.<sup>4</sup> The authors described that their quality assessment was carried out using a validated instrument and the process was explained. Quality criteria included randomisation, blinding, and the inclusion of reasons for participant withdrawals/dropouts.<sup>4</sup> The assessment of quality was blinded and carried out by the same two independent reviewers, and differences were resolved by consensus. There were seven trials on glucosamine and the mean quality score of the glucosamine trials was 90%.<sup>4</sup> There were eight trials on chondroitin and the mean quality score was lower at 68.4%.<sup>4</sup>

## Results of review by Richy et al.

The review by Richy et al. looked at several outcomes or effects of these two complementary therapies. These include one quantitative measure, joint space narrowing (JSN) and several qualitative measures: Lequesne Index (LI), WOMAC (Western Ontario MacMaster University Osteoarthritis Index), visual analogue scale (VAS) for pain, and it also investigated the safety profile of these therapies. Joint space narrowing from glucosamine was evaluated using data from two three-year trials (212 and 202 patients). When converted to natural units, the potential minimal joint space narrowing difference between glucosamine sulphate (GS) and placebo was found to be 0.27 mm (95% CI, 0.13-0.41 mm) after administration of 1500 mg daily for three consecutive years. The authors stated there was homogeneity between the results of the two trials. However they also pointed out that, using a different effect size scale by Cohen, the activity of glucosamine sulphate was rated as low to medium. The dropout rates of the two trials were also quite high (34% and 42.5%). Conventionally it is preferable this rate be less than 20%.<sup>26</sup> This higher dropout rate is most likely due to the duration of the trials being three years. Investigation of the initial RCTs found that one was carried out

in the Czech Republic (Pavelka et al., 2002) and the other in Belgium (Reginster, 2001) and both studies used a powder form of glucosamine.<sup>27,28</sup> The methods of both RCTs were described in detail and radiography was carried out using a highly standardised protocol, including the weight bearing x-ray with the knee in full extension and an antero-posterior approach.<sup>27,28</sup> The trained independent readers of the x-rays were blinded to treatment assignment.<sup>27,28</sup> However, it did not state whether the readers were qualified radiologists. The radiography in the trial by Pavelka (2002) was carried out by the same technician using the same machine at year 1, 2, and 3, which was strength of the study.<sup>27</sup> It should be noted that the same two RCTs were also analysed in the Cochrane review by Towheed et al.

At the time of the literature search, Richy et al. stated that there were no detailed, long-term, randomised controlled trials about joint space narrowing with chondroitin therapy; therefore they could not include an analysis on the structural benefits of chondroitin.<sup>4</sup>

Richy et al. (2003) found highly statistically significant improvements in four outcomes (Lequesne index, WOMAC, VAS and mobility) for glucosamine when compared with baseline and with VAS and mobility for chondroitin.<sup>4</sup> No placebo group reached significance in any of these outcomes. In regards to pain reduction assessed by VAS, the global effect size for glucosamine and chondroitin was modest at 0.49 (95% CI, 0.31-0.67; P for association <.0001).<sup>4</sup>

Richy et al. found a relative risk of being a responder when allocated to glucosamine or chondroitin versus placebo was 1.6 (95% CI 1.38-1.82).<sup>4</sup> Being a responder was defined by the authors of each RCT or based on global assessment by Richy and fellow researchers. Secondary calculation of the relative risk of response gives a figure of 1.7 for chondroitin and 1.3 for glucosamine.

In all 15 trials in this meta-analysis, rescue analgesia with NSAIDs was permitted. The authors stated that in most of the trials there was a cumulative low dose of NSAIDs.<sup>4</sup> Specific data on the doses and frequency of rescue analgesia were not presented by Richy and fellow authors. As rescue analgesia was likely to be a confounding factor in measures of pain reported by the patients, these data should have been made available in the review. The authors stated that both the placebo group and groups assigned to chondroitin or glucosamine were allowed rescue medication.<sup>4</sup> This shows the groups were treated equally; however there would have been wide ranging differences in patient's

self administration of NSAIDs. Richy et al. found that those assigned to glucosamine or chondroitin used a lower quantity of rescue analgesia over the study period compared to participants taking placebo. Despite this lower consumption of pain relief, those assigned to either active ingredient still reported less pain than those people receiving placebo.<sup>4</sup> The Cochrane review and a network meta-analysis by Wandel et al. did not discuss rescue analgesia at all in their papers. This is a major weakness as it is a confounding factor and it is likely that some if not most RCTs in their reviews allowed rescue analgesia.<sup>3,6</sup> Wandel et al. did make recommendations for further trials including the careful control and monitoring of analgesic co-interventions; however more indepth discussion was warranted.<sup>6</sup>

## Critical appraisal of network meta-analysis by Wandel et al.

In 2010, Wandel et al. published a network meta-analysis analysing the effects of glucosamine, chondroitin or placebo in patients with osteoarthritis of the hip or knee.<sup>6</sup> The review evaluated 10 trials with a total of 3803 participants.<sup>6</sup> Out of the three reviews critically appraised, Wandel had the second highest number of participants after Towheed.<sup>3,6</sup> Similar to Towheed, 80% of trials investigated OA of the knee exclusively (8 of 10 RCTs).<sup>3,6</sup>

The inclusion criteria of Wandel et al. were similar to the other two reviews which have been discussed. However they excluded trials with less than an average of 100 patients per arm.<sup>6</sup> This study also included RCTs which were published until June 2009, making it the most up to date of the three reviews. It also searched as far back as inception (like Towheed) whereas Richy et al. restricted RCTs to those published from 1980.<sup>3,4,6</sup> This network meta-analysis carried out a quality assessment, where two of the four reviewers independently assessed concealment of allocation, blinding and adequacy of analyses.<sup>6</sup> However, the quality assessment did not state that the reviewers were blinded to author, title and other identifying details of the RCTs; therefore it must be assumed that blinding was not carried out. This review required that RCTs had either used a formally approved preparation of the CAM or had confirmation of its contents from laboratory analysis.<sup>6</sup> This quality control measure is a strength of this meta-analysis.

## Results of network meta-analysis by Wandel et al.

Wandel et al. included six trials which investigated joint space narrowing (JSN) in their review. Three investigated glucosamine sulphate solely, two chondroitin and one investigated a combination of glucosamine hydrochloride and chondroitin sulphate.<sup>6</sup> The two trials on JSN included in the review by Richy et al. and Towheed et al. were also included in this review.<sup>4, 6</sup> Wandel et al. found minute effects for all preparations (glucosamine, chondroitin and combination) on joint space narrowing compared to placebo.<sup>6</sup> The difference reported for glucosamine was -0.2 mm (-0.3 to 0.0 mm) in favour of glucosamine, which corresponds to an effect size of -0.16 (-0.25- 0.0). Heterogeneity between trials was reported as low. With a lower end of the 95% confidence interval (CI) equalling zero or the line of no effect, Wandel et al. concluded that the effects of glucosamine on joint space narrowing are minimal. This differs to the results of Richy et al. who used global effect size as a measure, and found the effect of glucosamine to be low to medium. Richy et al. chose to look upon these results more favourably by focussing on the actual change in mm, which was 0.27 mm, and the CI did not cross the line of no effect (zero).<sup>4</sup> Wandel et al. found differences reported for chondroitin and the combination were still in favour for these active ingredients compared to placebo; however the effect sizes were lower than that of glucosamine and both 95% CIs overlapped zero.<sup>6</sup> Considering there were only three RCTs investigating glucosamine and JSN published by June 2009 that met inclusion criteria for this review, more high-quality, longer-term studies are needed.

For pain outcomes, Wandel et al. took a slightly different approach to the other reviews. The authors refer to a hierarchy of pain outcome measures published in 2006 by Jüni et al. with global pain scale being the highest in the hierarchy.<sup>6, 29</sup> When more than one pain outcome was reported in an RCT, only the highest ranked measure was included in the meta-analysis.<sup>6, 29</sup> Using this method, Wandel et al. found that there was no clinically significant difference in global pain score (VAS) with glucosamine, chondroitin, or the combination compared to placebo. The authors did state that there was abundant statistical power in VAS figures; however a pre-specified minimal clinically important difference of -0.9 cm on a 10 cm VAS was not reached by any of the pooled estimates.<sup>6</sup> The overall difference

in reported VAS with supplement versus placebo was -0.4 cm (95% CI -0.7 to -0.1 cm) on a 10 cm VAS for glucosamine, -0.3 cm (95% CI -0.7 to 0.0 cm) for chondroitin, and -0.5 cm (95% CI -0.9 to 0.0 cm) for the combination of glucosamine and chondroitin. The biggest difference was seen with combination, followed by glucosamine and then chondroitin.

As mentioned earlier, there are possible confounding factors that may lower our confidence in the results of trials or reviews on the efficacy of glucosamine. Wandel et al. carried out tests for interaction, which help examine whether an effect is modified by another variable.<sup>6, 30</sup> Confounding factors that were tested included: quality of the RCTs, type of joint (knee, hip, etc.), type of glucosamine (GH or GS), presence or absence of quality control measures for supplements.<sup>6</sup> The authors found that the tests for interaction were negative for these four variables ( $P \geq 0.20$  for interaction).<sup>6</sup> The inclusion of this statistical analysis was a strength of the review.

## Safety profile

All three reviews found no significant difference in the number of side effects reported by those on glucosamine compared to placebo.<sup>3, 4, 6</sup> The Cochrane review reported that side effects mainly included stomach upset and other joint pain.<sup>3</sup> A study by Reginster (2001) included in all three reviews found that the four most commonly reported adverse effects were abdominal pain, indigestion, diarrhoea and increased blood pressure.<sup>28</sup> The percentage of patients assigned to glucosamine reporting these symptoms was either equal to or lower than those reporting these side effects in the placebo group.<sup>28</sup>

Other research suggests that extra caution and closer monitoring may be necessary for people with:

- significant shellfish allergies, as glucosamine is prepared from shellfish and therefore may cause an allergic reaction;<sup>8</sup>
- diabetes, as glucosamine may increase glucose levels in patients with suboptimal glucose tolerance, making close blood sugar level monitoring advisable;<sup>8</sup> and
- warfarin use, as there have been 22 cases reported to the World Health Organisation of increased bleeding or bruising with the combination of glucosamine and warfarin.<sup>8, 31</sup>

## Conclusions

All three reviews are classed as Level 1 evidence and the strengths and weaknesses of each have been discussed. Due to differences in the spectrum of studies included in each review and the differing benchmarks set for positive results, there is not a clear consensus amongst the reviews on the efficacy of glucosamine for OA. The review by Richy et al. showed significantly better results for glucosamine over placebo for the Lequesne index, WOMAC, VAS pain and mobility. However the results reported by Wandel et al. regarding VAS were not found to reach a pre-specified minimal clinically important difference and therefore the authors' recommendations were that it should not be prescribed to patients, who have not received these treatments before.<sup>6</sup> When Towheed et al. analysed only high-quality studies, this review found that glucosamine was not significantly more effective than placebo in reducing pain in OA sufferers. However, it did find efficacy for glucosamine for reducing pain when both high- and lower-quality RCTs were analysed and when Rotta brand GS was investigated exclusively. The subgroup analysis of Rotta preparation found statistically significant benefit of GS over placebo on four outcomes: reduction in pain, Lequesne Index and WOMAC pain and function subscale scores.<sup>3</sup> This adds strength to the viewpoint that GS may be superior to GH. As Rotta is manufactured in Europe, where GS is a pharmaceutical, it is also more likely that the dose and formulation is as the label reads. GS is not considered a pharmaceutical in countries such as Australia, United States of America and Canada. When analysing the results of this Cochrane review, publication bias due to pharmaceutical company involvement should be considered and may decrease confidence in the validity of these results.

## Recommendations

The lack of consensus amongst reviews makes clear recommendations difficult, but patients considering the use of glucosamine could be informed that uncertainty remains as to whether glucosamine reduces the pain and disability of osteoarthritis and preserves cartilage compared with placebo. The advantages glucosamine may have are generally small and of a size that may not justify its cost. However it does seem to be safe, but care should be taken in patients with diabetes, those taking warfarin and those with allergies to shellfish. In patients who have been taking glucosamine and

have found it to be beneficial, there could be a case to continue it. There may be a difference in the effectiveness in different preparations of glucosamine, with the strongest evidence being for glucosamine sulphate preparations taken at a dose of at least 1500 mg per day.

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**Table 1. Results of the three systematic reviews on glucosamine**

	Towheed (2009) <sup>3</sup>	Richy (2003) <sup>4</sup>	Wandel (2010) <sup>6</sup>
CAM investigated	GS and GH versus placebo	GS, chondroitin versus placebo	GS, GH, chondroitin, combination versus placebo
OAsite investigated	80% RCTs studied knee	Knee OA exclusively	80% RCTs studied knee
Number of RCTS	25	15	10
N u m b e r o f participants (mean per trial)	4963 (198)	1775 (118*) (1020 glucosamine; 755 chondroitin)	3803 (380*)
Trial duration	Mean was 25.5 weeks	Mean for glucosamine: 51.4 weeks* [calculated from Table 2 <sup>4</sup> ] Mean for CS: 25.9 weeks* [calculated from Table 3 <sup>4</sup> ]	Trial duration ranged from: 4 weeks to 156 weeks. Data were extracted as multiple time points; therefore mean could not be calculated. See table 1. <sup>6</sup>
Publication dates incl. in literature search	Inception to January 2008	January 1980 to March 2002	Inception to June 2009
Pain	Analysis from 18 studies (high and low quality) showed 22% improvement in pain with glucosamine compared to placebo. (summary SMD -0.47; 95% CI -0.72 to -0.23). Post-hoc analysis (only 11 RCTs assessed as high quality): no significant difference in pain compared to placebo (summary SMD -0.16 95% CI -0.36 to 0.04) WOMAC pain did not reach statistical significance.	VAS (12/15 RCTs); Global effect size (random effects) was 0.49 (95% CI, 0.31-0.67; P for association <0.001)	VAS (10/10 RCTs) No clinically significant difference in global pain score (VAS) with glucosamine, chondroitin, or the combination compared to placebo. The overall difference in reported VAS with supplement versus placebo was -0.4 cm (95% CI -0.7 to -0.1 cm) on a 10 cm VAS for glucosamine, -0.3 cm (95% CI -0.7 to 0.0 cm) for chondroitin, and -0.5 cm (95% CI -0.9 to 0.0 cm) for the combination of glucosamine and chondroitin
Function	11% improvement in function reported by authors (based on the most representative study) (LI) WOMAC function did not reach statistical significance		NA
J o i n t s p a c e narrowing (glucosamine)	2 RCTs (Pavelka 2002; Reginster 2001) using Rotta preparation SMD measuring minimum JS width for the knee or hip was 0.32 (95% CI 0.05 to 0.58) after administration of 1500 mg daily for three consecutive years. Authors state statistically significant in favour of glucosamine and therefore glucosamine may have an effect on the radiological progression of OA.	2 RCTs (Pavelka 2002; Reginster 2001) using Rotta preparation potential minimal JSN difference between GS and placebo was found to be 0.27 mm (95% CI, 0.13-0.41 mm) after administration of 1500mg daily for 3 consecutive years Authors state highly significant (P<0.001) effect on minimum JSN	6 RCTs JSN difference -0.2 mm (95% CI -0.3 to 0.0 mm) in favour of glucosamine compared to placebo, which corresponds to an effect size of -0.16 (95% CI -0.25- 0.0).
J o i n t s p a c e narrowing (chondroitin)	NA	Quality of published RCTs on chondroitin and JSN deemed insufficient for inclusion in review	JSN difference -0.1 mm (95% CI -0.3 to 0.1 mm) in favour of chondroitin, compared to placebo, which corresponds to an effect size of -0.08 (95% CI -0.25 to 0.08)
J o i n t s p a c e narrowing (combination)	NA	NA	JSN difference 0.0mm (95% CI -0.2 to 0.2 mm) for the combination compared to placebo, which corresponds to an effect size of 0.00 (95% CI -0.16 to 0.16)
Relative risk of being a responder	NA	1.6 (when treated with glucosamine or chondroitin, 1.6 times more likely to have a positive response to treatment compared to placebo) (1.38 – 1.82)	NA
Absolute risk difference and NNT	NA	The absolute risk difference of being classified to allocated glucosamine or chondroitin or placebo is 20% Associated NNT is 4.87	NA
Safety	Glucosamine was as safe as placebo in terms of the number of participants reporting adverse reactions (RR 0.99; 95% CI 0.91 to 1.07) placebo group 4.7% were withdrawn because of toxicity 39% reported an adverse reaction glucosamine group 3.3% were withdrawn because of toxicity 30% reported an adverse reaction	Global relative risk (random effects) for presenting an adverse reaction when allocated to glucosamine or chondroitin compared with placebo was 0.80 (95% CI, 0.59-1.08; P for association =0.15)	Odds ratios of adverse events compared with placebo were: glucosamine: 0.94 (0.59 to 1.47), chondroitin : 0.99 (0.49 to 2.00), combination: no data available The odds ratios for withdrawals or drop-outs because of adverse events were: glucosamine: 0.99 (0.61 to 1.50); chondroitin: 0.92 (0.56 to 1.51); combination: 0.90 (0.43 to 1.85)

Key: CI= confidence interval; LI=Lequesne Index; NA=not applicable; JSN=joint space narrowing; NNT=number needed to treat; SMD= standardised mean difference; WOMAC=Western Ontario MacMaster University Osteoarthritis Index

\*calculated, not stated in review

Please note that in the network meta-analysis, Wandel et al. uses the terms “credible interval” and “confidence interval” interchangeably as these terms are analogous to each another

# The endocannabinoid system – the missing link in understanding pain?

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**Abstract.** The endocannabinoid system is an endogenous lipid signalling system in all vertebrates. It has multiple important functions including the modulation of pain and it could have a significant role in the future in the clinical management of both acute and chronic pain.

It consists of several receptors and ligands, with the most studied components being the receptors CB1 and CB2 and the endogenous ligands AEA and 2AG.

## Keywords

endocannabinoids, CB1, CB2, AEA, 2AG, THC. G protein coupled receptor

## Abbreviations

eCS: the endocannabinoid system:  
CB1: Cannabinoid receptor type 1  
CB2: Cannabinoid receptor type 2  
AEA: Arachidonylethanolamine or Anandamide  
2AG: 2 Arachidonylglycerol  
FAAH: Fatty acid amide hydrolase  
DAGL: diacylglycerol lipase  
MAGL: monoacylglycerol lipase  
GPCR: G protein coupled receptor  
THC: Δ9 tetrahydrocannabinol

## Introduction

Sometimes a major breakthrough in the understanding of basic cellular mechanisms occurs through research on seemingly esoteric matters. This probably applies to the pursuit of the psychoactive ingredient of cannabis. Following the discovery of Δ9-tetrahydrocannabinol (THC), further research has uncovered a lipid signalling system present in all vertebrates that is intimately involved in most aspects of homeostasis. The endogenous cannabinoid system (eCS) seems to modulate both acute and chronic pain, and investigation of it has provided insights into pain concepts including “allodynia”, “hyperalgesia”, “neuropathic pain”, and “stress-induced analgesia”. The eCS is also involved in a number of medical conditions, such as diabetes, obesity, eating disorders, and depression. This paper offers an introduction to the eCS from an historical discovery perspective and specifically as related to pain mechanisms.

## The chequered history of cannabis

Cannabis (there are at least two plant species – *Cannabis sativa* and *Cannabis indica*) has been used by Homo sapiens from pre-recorded history for food, fibre, spiritual and medicinal purposes. There is archeological evidence from China indicating the use of the seeds for food (about 6,000 BC) and for textiles (about 4000 BC).<sup>1</sup> The first written record of the use as a medicinal herb occurs in a Chinese pharmacopoeia that dates from 2700 BC.<sup>2</sup> The Hindu sacred text Atharvaveda (1200-800 BC) refers to cannabis as the “sacred grass” with a possible use in relieving anxiety.<sup>3</sup> In about 450 BC the Greek historian Herodotus wrote: “The Scythians, as I said, take some of this hemp-seed, and, creeping under the felt coverings, throw it upon the red-hot stones; immediately it smokes, and gives out such a vapour as no Grecian vapour-bath can exceed; the Scyths, delighted, shout for joy.”<sup>4</sup> Dioscorides, a Greek physician serving the

Romans in 40-90 AD, wrote about hemp as “making the stoutest of ropes and having medicinal properties when eaten” (Book III of *Materia Medica*).<sup>5</sup>

The fibres from cannabis and mulberry were first used by the Chinese for making paper around 100 BC. Eventually, this use of cannabis spread, reaching Europe around 600 AD.<sup>6</sup> In 1150 the Moors used cannabis in the first paper mill in Europe and the plant continued to be the main fibre in paper for the next 850 years. The first ill wind against cannabis occurred in 1484 when Pope Innocent VIII singled it out as an unholy sacrament of the Satanic mass.<sup>7</sup> Between 1500 AD and 1800 AD cannabis production was encouraged, mainly to supply canvas and ropes for military purposes.

In more recent times (1839) Dr W B O’Shaughnessy (who was the first to introduce the concept of intravenous electrolyte therapy) investigated the medicinal uses of cannabis while working in India.<sup>8</sup> He reported it was effective for several conditions including pain, and cannabis soon became an accepted

component of Victorian medical treatment. A similar use of cannabis for pain was also reported in the first edition of the *Lancet*, where Queen Victoria's personal physician, Sir Russell Reynolds, had prescribed the Queen a cannabis extract for menstrual cramps and stated that "when pure and administered carefully, is one of the most valuable medicines we possess".<sup>9</sup>

In 1895 the Indian Hemp Drugs Commission concluded that cannabis had some medical uses, no addictive properties and a number of positive emotional and social benefits.<sup>3</sup> However the winds of prohibition were forming in both the USA and elsewhere. In 1915 Utah and California outlawed cannabis, followed by Texas in 1919,<sup>10</sup> mainly for racial reasons. At the 1924 Second International Opiates Conference Egyptian delegates claimed that cannabis usage was associated with serious social and health issues and called for international controls.<sup>11</sup> It was declared a narcotic and controls were recommended to governments. The UK banned cannabis in 1928. In the USA, lobbying by the FBI and newspaper magnate William Randolph Hearst, resulted in a heavy tax being placed on hemp production—effectively destroying the industry. Anslinger of the Federal Bureau of Narcotics described marijuana as "the most violence causing drug known to man".<sup>12</sup> In 1938 he planted sensational claims in Australian newspapers that "A Mexican drug that drives men and women to the wildest sexual excesses has made its first appearance in Australia. It distorts moral values and leads to degrading sexual extravagances".<sup>13</sup> By renaming cannabis as marijuana, US prohibitionists such as Anslinger were able to promote it as a new drug menace even though cannabis had been planted by the First Fleet convicts and there were many hectares of it growing wild in the Hunter Valley area and in Queensland.<sup>14</sup>

In that era there were many over-the-counter remedies available in Australia that contained cannabis extracts, including a popular mixture called "chlorodyne", which consisted of 6 grams of black Nepalese hash topped up with morphine and chloroform.<sup>15</sup> Cannabis cigarettes were also freely available. However, continued sensationalised claims in the mass media and pressure on politicians by the Council of Churches resulted in the plant being declared a noxious weed in late 1938.<sup>14</sup> It was eventually classified as a class 1 drug alongside heroin, LSD, cocaine and amphetamines.

Whilst the active ingredient of opium was known by 1804, the search for the active ingredient of cannabis remained unsuccessful until 1964 when an Israeli

research team successfully isolated and synthesised tetrahydrocannabinol as the biologically active component.<sup>16</sup> Then using the simple lock and key model proposed by Emil Fischer<sup>17</sup> the search was undertaken to find the cannabinoid receptors and the endocannabinoids, akin to the opioid receptors and endorphins. The first receptor, called CB1 was discovered in 1988.<sup>18</sup> CB1 was located in parts of the brain involved with movement, emotions, memory, pain modulation, appetite and reward systems and was found to be largely absent in the brain stem. A second receptor, CB2, was discovered in 1993<sup>19</sup> and it was located primarily in the immune system, peripheral nervous system, skeletal system and the internal organs.

The first endogenous cannabinoid, arachidonylethanolamide (AEA) or Anandamide (a Sanskrit word meaning *blissful amide*) was found in 1992 by Mechoulam, the team who had originally discovered THC.<sup>20</sup> His laboratory also discovered a second endocannabinoid, called 2-arachidonylglycerol (2-AG) in 1995.<sup>21</sup> There has since been an exponential increase of research into this newly discovered system. In addition to pain modulation, it has been found to be involved in a multitude of physiological functions from embryo implantation, energy and temperature homeostasis, to feeding and body mass control, in addition to other significant actions.

## The basics of the endocannabinoid system

### The ligands

It remains uncertain how many endocannabinoids exist in the body. Six have been identified, of which the best described are AEA and 2AG. The synthesis of both occurs in lipid rafts in the cell membrane, with AEA being formed when arachidonic acid is joined to the ethanolamine part of phosphatidylethanolamine.<sup>22</sup> AEA is then cleaved off by phospholipase D. 2AG is formed from diacylglycerol. Neither is stored. They are formed and released in response to increased calcium levels in the cell following depolarisation.<sup>23</sup> This is in contrast with other neurotransmitters which are stored and released from vesicles. Whereas AEA binds primarily to the CB1 receptor in the brain, 2AG binds to both CB1 and CB2 and is also the more common of the two.<sup>23</sup> These receptors are described

in the next section.

NADA (N-arachidonyl-dopamine) discovered in 2000 also preferentially binds to CB1 and like AEA is an agonist for the vanilloid receptor subtype 1 (TRPV).<sup>24</sup> The next endocannabinoid, called 2 arachidonyl ether or Noladin ether, was discovered in 2001.<sup>25</sup> It binds primarily to CB1. Virodamine (also called OEA) is the fifth endocannabinoid and is a full agonist of CB2 and partial agonist of CB1. It occurs in the brain at similar concentrations to Anandamide but at 2-9-fold higher levels peripherally.<sup>26</sup> The most recently found endocannabinoid is lysophosphatidylinositol (LPI) which acts on a third endocannabinoid receptor-GPR55.<sup>27</sup>

### The receptors

The cannabinoid receptors belong to the G protein coupled receptor superfamily.<sup>28</sup> They are metabotropic receptors, or, receptors coupled to metabolism and thus are relatively slow to cause an effect. This is in contrast to the ionotropic receptors which allow rapid movement of ions.

There are at least five CB receptors, with CB1 and CB2 being the most studied.

CB1 is located primarily in the central nervous system, especially the cerebellum, hippocampus and basal ganglia.<sup>29</sup> It is the most widely expressed GPCR in the mammalian central nervous system, and it is highly conserved across mammalian species with an amino acid homology of 81% between humans and rats.<sup>30, 31</sup> It also has been found in the lungs, liver and kidneys.<sup>32</sup> Activation of CB1 receptors by THC and synthetic cannabinoids causes a classic tetrad of behavioural effects in rodents of catalepsy, hypothermia, analgesia and hypomotility.<sup>33</sup>

CB2 receptors are expressed mainly on T cells of the immune system, on macrophages and B cells, and in haematopoietic cells. They are also expressed on peripheral nerve terminals in the dorsal root ganglion, and the neurons and glial cells in the CNS.<sup>34</sup> When activated these receptors modulate immune cell migration and cytokine release.<sup>35, 36</sup>

For the sake of completeness the other receptors are GPCR 18, 55 and 119. Less is known about their ligands and their function with some evidence however that LPI may be the ligand for GPCR 55.<sup>27, 37</sup> GPR119 occurs predominantly in the pancreas and GI tract and seems to be involved in regulation of incretin and insulin secretion.<sup>38</sup>



# Retrograde signalling

The basic mechanism of action is:

- Following a sudden increase of intracellular calcium levels in the **postsynaptic** neurone, from depolarisation, or receptor activation by glutamate or GABA there is an increase in synthesis of 2AG or AEA.
- Release of these occurs into the synaptic cleft with diffusion to the **presynaptic** neuron terminal CB1 or CB2 receptors.
- Several steps occur that include the opening of K<sup>+</sup> ion channels and the closing of Ca<sup>++</sup> channels
- The net effect being a transient or a prolonged reduction in release of the **presynaptic** neurotransmitters<sup>39</sup>

There can be two different outcomes from this action, depending on the type of incoming signal – either a suppression of excitatory signals, mediated by glutamate, or a suppression of inhibitory signals which are mediated by GABA.<sup>40</sup> The former has been called depolarisation-induced suppression of excitation (DSE) whilst the later is called depolarisation-induced suppression of Inhibition (DSI).

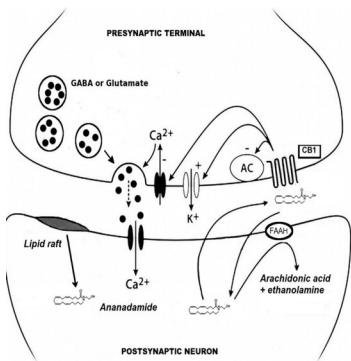


Figure 1. Retrograde transmission  
Abbreviations: AC – adenyl cyclase FAAH – fatty acid amide hydrolase

Breakdown of both these endocannabinoids occurs rapidly with separate enzymes involved. Anandamide is inactivated by FAAH and 2AG mainly by monoacylglycerol lipase.

## Endocannabinoid system and pain

The components of the eCS are present in key regions involved in the detection, relay and integration of nociceptive inputs, such as the skin, dorsal root ganglia, spinal cord, periaqueductal grey and rostral ventromedial medulla. Converging

evidence supports a significant role of endocannabinoids in the tonic inhibition of pain responses and the setting of nociceptive thresholds.

Rodent models have been used extensively to investigate the role of eCS relating to acute or to chronic pain. Those that involve injecting carageenan or formalin into the hind paw pad and determining the effect on the eCS are the acute pain models. What is considered a neuropathic pain model involves partial ligation of spinal nerve roots or the sciatic nerve.

A summary table of some of these studies is as follows:

Table 1. The eCS in rodent models of pain<sup>41</sup>

Model	AEA	2AG	Note
Formalin	No change	Decrease	
	Decrease	Decrease	
Carageenan		Decrease	
Spinal nerve ligation	Rat L5 DRG	Increase	On day 14
	Rat spinal cord	Increase	On day 14
	Rat thalamus	Nochange	On day 14

Whilst there is little of practical value in the above table, using these models has formed the basis of the studies into the effects of the different synthetic ligands, blockade of FAAH and DAGL and the other components of the eCS pathway.

In summary some of these studies are as follows:

Table 2. Effect of administered eCS components in rat models of pain<sup>42</sup>

Component used		Model of pain	Outcome
AEA	Rat	Thermal allodynia	Reduced hyperalgesia
2AG	Mouse	Chronic construction injury	Inhibition of proinflammatory cytokines
AEA/2AG	Rat	Chronic construction injury	Antinociception
FAAH inhibition	Mouse	Chronic construction injury	Decreased allodynia
FAAH inhibition	Mouse	Mechanical allodynia	Decreased allodynia
Δ9THC	Rat	Thermal allodynia	Antinociception

There is little debate that the eCS can have multiple effects relating to pain, including modulating neuronal, glial and immune cell functions with anti-excitotoxic, anti-inflammatory and vasodilatory effects. These effects occur at the spinal, thalamic and also at peripheral sites.<sup>42</sup> In the models of acute pain, cannabinoids are equally as effective as opioids against thermal, mechanical and chemically induced pain.<sup>43</sup> In the models of chronic pain, both inflammatory and neuropathic, cannabinoids are possibly superior to opioids.<sup>44</sup> For a comprehensive review of this aspect see Zogopoulos et al.<sup>42</sup>

## Current clinical applications relating to the eCS

Whilst the current applications of the research is quite limited, a few pharmacological agents have been released for clinical use.

These include:

**Rimonabant.** This is a selective CB1 receptor inverse agonist. It was introduced for treatment of obesity and smoking cessation. Subsequently it was withdrawn from clinical use due to adverse side effects including depression. Rat studies however found that it markedly reduces thermal hyperalgesia and mechanical allodynia.<sup>45</sup>

**Palmitoylethanolamine (PEA).** This is a naturally occurring amide present in some foods including egg yolk and peanuts. It has been known to mimic endocannabinoid actions even though it does not bind to CB1 or CB2. PEA has affinity for the less studied GPCR55 and GPCR119 and also has effects on peroxisome proliferator-activated receptor alpha but there may be an entourage effect on levels of AEA.<sup>46</sup> It has been shown to have anti-inflammatory, anti-nociceptive and anti-convulsant effects.<sup>47, 48, 49</sup> PEA is not registered as a therapeutic agent in Australia but it can be imported for individual use. It is available online from the Netherlands where it is registered as a food supplement.

**Nabiximols (Sativex).** This is an oromucosal spray consisting of a THC and cannabidol

roughly in a 1:1 ratio and is both a CB1 and CB2 receptor agonist. It has been prescribed to patients in the UK, and several other countries, for the treatment of spasticity and neuropathic pain in multiple sclerosis (MS). Whilst it has also been approved by the Therapeutic Goods Administration in Australia for muscle spasticity associated with MS, state laws regarding cannabis have created some uncertainty as to clinical use here. Trials indicate that in patients with multiple sclerosis, spinal cord injury, brachial plexus damage and limb amputation there is significant pain relief.<sup>50</sup>

**Dronabinol.** This is an oral THC formulation. It is registered in Australia for use by HIV patients to counteract sarcopenia. In clinical trials it significantly reduces pain compared to placebo with the number needed to treat of 3.5.<sup>51</sup>

**Nabilone.** This synthetic cannabinoid mimics the actions of THC and it has been used mainly as an anti-emetic agent. Clinical trials have failed to determine any useful analgesic activity.<sup>52</sup>

**Paracetamol and COX2 inhibitors.** Although paracetamol has been used as an analgesic and antipyretic for over 50 years, the mechanism of action has been largely unknown until recently.<sup>53</sup> It is conjugated to arachidonic acid to form N-arachidonylphenolamine by FAAH. This acts as a TRPV1 agonist and it prolongs the action of AEA by inhibiting re-uptake.<sup>54</sup> The COX2 inhibitors also function by inhibiting FAAH with Ibuprofen being found to potentiate the effect of exogenous cannabinoids.<sup>55</sup>

## Conclusion

The eCS is an emerging field in the management of both acute and chronic pain. It is contributing to our understanding of both these conditions and it provides an avenue for research into developing more effective treatments. Currently the clinical applications are quite restricted but it is undoubtedly “early days”. One would also speculate as to the existence of endocannabinoid related diseases and wonder if fibromyalgia/chronic fatigue could be in that category.

As the eCS is probably novel to many physicians it has been simplified with much omitted. More in depth reviews are by Zogopoulos<sup>42</sup> and Guindon.<sup>56, 57</sup>

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# Discogenic back pain: An historical perspective

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**Abstract.** Since early times low back pain with radicular leg pain has been described by medical authorities, including Hippocrates, Schmorl and Dandy. However, the causal relationship between the disc and radicular leg pain was only first clearly made in the seminal article on disc herniation by Mixter and Barr in 1934. Key discoveries in history which helped establish our understanding of discogenic back pain are presented in this article.

## Method

Using Pubmed a search was undertaken to locate the relevant medical literature. Search terms, including discogenic back pain, discovery of causes of back pain, and historical perspective low back pain, were applied.

Articles that seemed to be significant were sourced from the Peninsula Health Library. Any relevant articles that were discovered by cross-reference were also perused where available. Some of the literature was reviewed only in abstract form.

## Introduction

In 2003 the total economic burden of low back pain (LBP) in Australia was estimated at \$A9.17 billion.<sup>1</sup> LBP affects 85% of the Australian population during their lifetime, with about half recovering within a two-week period and three quarters recovering within a month.<sup>2,3</sup> Croft (1998) suggested however that only a small minority of patients will completely recover from LBP.<sup>4</sup>

While about 30-50% of mechanical low back pain cases are caused by pathology of the intervertebral disc<sup>5</sup> (the other causes include degenerative zygoapophysial joints, sacroiliac joints, trigger points, myofascial pain etc) only about 5% of cases are due to actual disc herniation.<sup>6</sup>

The idea of discogenic pain, or even the spine, being the underlying cause of LBP is a commonly accepted differential today; however this was not always the case. This article reviews, from an historical perspective, the discovery of the discal aetiology of LBP.

## Discussion

There is archeological evidence that LBP has afflicted humans for millennia, including the fossil remains of a Neanderthal man with evidence of degenerative changes in the vertebrae.<sup>7</sup> In ancient Egypt (about 1500BC) a papyrus on the topic of back pain records the following: "If thou examines a man having a sprain of the vertebra of his spinal column, thou shouldst say to him: extend now your legs and contract them both. He contracts them both immediately because of the pain he causes in the vertebra

of the spinal column in which he suffers. Thou shouldst say to him: one having a sprain in the vertebra of his spinal column an ailment I shall treat. Thou shouldst place him prostrate on his back..."<sup>8</sup> The sentence is unfortunately incomplete and subsequently we remain uncertain as to the author's proposed treatment for this possible case of LBP and radicular leg pain. The Greeks and Romans also documented back pain and possible treatments but little further insight was made into the underlying pathology.

By the 1700s LBP was classified as a form of rheumatism.<sup>9</sup> "Rheuma" is a Greek word meaning "a watery discharge" stemming from the brain and precipitating pain in joints around the body.

Scudamore published that chronic rheumatism could be devoid of "fever but aggravated by motion" and attributed the cause to inflammation of the white fibrous tissue of the body.<sup>10</sup> As suggested by Scudamore, the term "rheumatism" was then used as an umbrella term to describe conditions like LBP, acute rheumatic fever and arthritis.

In the 1800s physicians began to seek the actual cause of LBP. One concept was that it might be due to the accumulation of "rheumatic phlegm" in muscles, and methods such as cupping and relieving a patient of constipation were some of the contemporary treatments.<sup>11</sup>

Others felt that cold and damp environments were causative factors,<sup>12, 13</sup> and there were many different treatments proposed.

## Spine and trauma as origin of back pain

Dr James Brown of the Glasgow Royal Infirmary published a paper in 1828 on "Irritation of the spinal nerves" and seems to be the first to connect the vertebral column and nervous system as the aetiology of LBP.<sup>14</sup> He established one of two important concepts regarding back pain in the 19th century – that back pain could originate from the spine. The second important concept was that it could arise from *trauma* to the spine. This had emerged with the advent of the industrial revolution and the building of the railways. Railway collisions were common and victims sometimes developed back pain especially if sitting facing away from the direction of impact. A correlation with trauma was made, and back pain even came to be known as "railway spine".<sup>15</sup>

## Sciatica

An early clinical description of sciatica is provided by Hippocrates. He uses the word "ischiatric" to describe a condition that afflicts men between ages 40 and 60 with radiated pain to the foot.<sup>16</sup> He observed that this radiation was associated with more favourable outcomes compared to hip pain. This is probably a reference to osteoarthritis of the hip which tends to have a more chronic natural history, while radicular leg pain often resolves.

In the early Indian texts, physicians reflected that injury to the lumbosacral region (called kakundram marma) could cause loss of sensation and paralysis in the

lower extremities.<sup>17</sup>

The first book on sciatica was published in 1764 by Domenico Cotugno. He felt that sciatica might be due to an accumulation of fluid around the sciatic nerve<sup>18</sup> and he used a treatment of “aqua-puncture” which consisted of aspirating fluid. Regardless of this treatment, he did correctly make the connection between anatomical structure and clinical symptoms.

Between 1764 and 1878 only 11 postmortem studies of sciatica were published. The non-fatal nature of sciatica and contemporary religious constraints may have contributed to this paucity of study into the underlying pathology. In 1905 however there is an account of a postmortem examination of a labourer with sciatica by Dr Ramsay Hunt. He reported a gelatinous deposit in the sciatic nerve, without evidence of macroscopic or microscopic inflammation. There is no report of Hunt actually exploring the contents of the vertebral canal, where he may have discovered evidence of a herniated disc.<sup>19</sup> Schmorl, a contemporary German physician, had identified prolapsed disc material in the spinal canal in other postmortems; however, he believed these were asymptomatic in life.<sup>20</sup>

With regards to historical treatments for radicular leg pain, some interesting and unusual records exist. These include reports from Derbyshire, where the legs of people with sciatica would be treated with the smoke created from burning ferns<sup>21</sup> and people in Exmoor would use incantations.<sup>22</sup>

## Anatomical descriptions

The first adequate anatomical description and illustration of a prolapsed vertebral disc was provided by Luschka in 1858. He described a prolapsed disc with stretching of the posterior longitudinal ligament and nerve root compression.<sup>23</sup> In 1929, Andrae and Schmorl described postmortem studies in which they found evidence of disc herniation through the posterior longitudinal ligament and also through the endplates of the vertebral bodies. The latter are now known as Schmorl’s nodes.<sup>24, 25</sup>

## Current concepts of discogenic pain

Goldthwaite, Middleton and Teacher, Dandy, and Mixter and Barr are probably the most important historical figures who have established the modern understanding

of discogenic back pain.

Goldthwaite (1911) documented a clinical case in which he suggested that compression of a nerve at the lumbosacral joint may be implicated in the paresis suffered by a patient post-manipulation. This basic notion was supported by other contemporary accounts.<sup>26, 27, 28</sup>

Middleton and Teacher (1911) furthered the understanding of low back pain aetiology by describing a case of low back pain and linking it with potential sequelae. The case was of a patient who had known back pain and central disc prolapse, who subsequently developed a fatal paraplegia.<sup>29</sup>

Dandy (1929) not only described a case of paraplegia caused by disc herniation, but established histological evidence. He described histological findings of a prolapsed nucleus pulposus and the associated neurological deficits.<sup>30</sup>

However, it was Mixter and Barr (1934) who fundamentally changed the understanding of sciatica and they are the paramount historical figures who accurately described the relationship between the intervertebral disc protrusion and radicular leg pain.

William Mixter was a Boston neurosurgeon, and Joseph Barr was an orthopaedic surgeon. They asserted in 1934 that posterior disc damage could lead to extrusion of the nucleus pulposus, which in turn could compress the contents of the spinal canal and cause radicular leg pain. This idea had developed from a discussion of a clinical case between Mixter and Barr in the hallway of the Massachusetts General Hospital. The case was a patient who developed left-sided radicular leg pain after a skiing accident in 1930. His symptoms subsided with bed rest but had recurred two years later. The patient had consulted with an associate of Mixter, Dr F Ober, who was of the opinion that the patient would not benefit from manipulation of the lumbar spine and the symptoms were due to a possible spinal mass. The patient was referred to Mixter, who had an interest in spinal tumours. Mixter performed an explorative laminectomy, with findings which he considered to be a chondroma. Joseph Barr who had an interest in the work of Schmorl, postulated however that this lesion might not be a chondroma but be comparable to the posterior disc herniation described by Schmorl. Mixter and Barr then found a similar case reported by a pathologist, Dr. Charles Kubik, who noted that the extruded material in a patient with a chondroma was histologically normal.<sup>31</sup> Hence the extruded material was unlikely to be a tumour. Mixter and Barr compared the histological specimens of other supposed chondromas and normal discs

and found that most of the specimens were in fact normal cartilage. They changed the diagnosis of chondroma to the term familiar to clinicians today of “disc herniation”.<sup>32</sup>

The idea gained momentum in the medical profession after publication in the *New England Journal of Medicine* (Mixter and Barr, 1934). The Mixter and Ayer paper of 1935 also deserves mention, as it highlighted the idea that disc pathology should be considered as a differential in low back pain even in the absence of radicular pain and radiculopathy.

## The tyranny of the disc

Over the next few decades after the seminal Mixter and Barr paper, there was a dramatic surge in the surgical removal of discs performed by both neurosurgeons and orthopaedic surgeons. These were often unsuccessful, sometimes with dire consequences for patients.<sup>33</sup> The modern approach to discectomies is that they are performed primarily for LBP with prominent radicular symptoms.

## Non-discogenic back pain

Whilst this paper is an historical reflection on disc pain it is important to recall that in approximately 85% of cases of low back pain, a diagnosis of “nonspecific low back pain” is often made without any real attempt to determine an underlying cause.<sup>34, 35</sup>

The other structural causes of LBP include facet syndrome,<sup>36-42</sup> symptomatic degenerative change,<sup>43-45</sup> instability,<sup>46, 47</sup> trigger points and myofascial pain<sup>48</sup> and these should all be considered instead of the diagnosis of “nonspecific low back pain”.

In treating patients with LBP associated with radicular pain or radiculopathy, disc pathology is usually the underlying aetiology.

## Conclusion

LBP is a condition with a high lifetime prevalence. It is an interesting exercise to review historically the development of our understanding of the underlying pathology and to appreciate the work of the early medical practitioners. Whilst there is now better understanding of the causes of LBP, radicular pain and radiculopathy, treatment is still problematic for many patients and

this is the area in need of progress. No doubt there are practitioners currently active in the field who will become historically important with contributions to our understanding of the condition. One such Australian figure is Professor Nik Bogduk.

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# The foundations of myofascial pain and dysfunction – a tribute to Dr Janet Travell

*Dr Peter Jackson*

*“Life is like a bicycle – you don’t fall off until you stop pedalling”*

## *Dr Janet Travell 1901-1997*

Many practitioners of musculoskeletal medicine will have been influenced by, or at least aware of, the work of Dr Janet Travell. She had a remarkable career pioneering a considerable body of knowledge and treatment of myofascial pain. Here is a brief biographical tribute to her life and works.

Her father was a practising physician for 60 years and both Janet and her sister followed their father into a career in medicine. She graduated from Cornell University Medical College in New York City in 1926, receiving the award for the highest scholastic achievement. She then spent two years as a resident at New York Hospital whilst also acting as the ambulance surgeon to the New York police force.

This was followed by a research fellowship at Bellevue Hospital studying the effects of digitalis on patients with lobar pneumonia, before she returned to Cornell to the department of pharmacology, where she was eventually appointed professor. Prior to her seminal interest in musculoskeletal disorders she was also a cardiac consultant at Sea View Hospital on Staten Island (1936) and at the Cardiac Clinic at Beth Israel Hospital.

In 1940, at the age of 38, she developed a chronic painful and stiff shoulder and arm while she was involved in teaching, directing special research projects for pharmacology students and participating in 24-hour laboratory experiments. She considered that the painful shoulder and arm muscles were subsequent to the longhand writing of laboratory procedures and results. Self-examination of her shoulder girdle muscles revealed tender points which when palpated intensified or reproduced her pain. She realised there was no direct neural connection between these loci in her upper extremity and thus began her lifelong interest in myofascial pain.

Her symptoms reminded her of the 1936 paper entitled “Persistent Pain in the Shoulder Region Following Myocardial

Infarction”<sup>1</sup> in which the authors reported an incidental finding that two of their patients had a so-called trigger zone in the scapular region, pressure over which caused them an increase in pain. One patient had discovered that pressure over the scapula produced a pain that radiated to the left shoulder, down the left arm and up the left side of the neck. These authors noted that “treatment was singularly ineffective”. In this era, prior to the Second World War, acute myocardial infarction was treated mainly with prolonged bed rest and it was complicated by 10-20% prevalence of intractable shoulder-arm pain syndrome.

Whilst many of her patients at Sea View had life-threatening pulmonary disease, some complained more about pain in the shoulders, separate from their main condition. Systemic palpation of their scapulae and chest musculature uncovered the presence of trigger areas similar to her own.

Physicians at the time were familiar with the term “fibrositis” introduced by Sir William Gowers<sup>2</sup> in 1904. This term referred to local tenderness and regions of hardness in a muscle. Gowers considered this to be an inflammatory condition but biopsy had failed to support such pathology. However, Kellgren<sup>3</sup> in a 1938 *British Medical Journal* article, “Referred Pain from Muscles”, reported that injecting hypertonic saline into different anatomical areas including fascia, tendons and muscle produced pain patterns that differed not only in quality but also had specific referral patterns. Other contemporary published works include Albee (1929)<sup>4</sup> who introduced the term “myofascitis” and Steindler (1939)<sup>5</sup> who coined the term “myofascial pain and trigger point”. She possibly was also aware of the work of Michael Kelly in Australia.

Using this background knowledge, she instructed her then resident to inject tender loci in the chest and scapular regions of her patients and she was able to secure some

prompt and lasting pain relief, with return of normal range of motion at the shoulder joint. She then persuaded her father to inject her own dysfunctional shoulder muscles and also had a good outcome.

In 1941 she extended her study of referred skeletal muscle pain to include patients at the Beth Israel Hospital.

Microscopic examination of biopsied muscle had not revealed pathological change but she noted that merely touching or lifting the skin covering the muscle at the trigger area or pinching the interstitial fascia with forceps instantly caused pain in the reference zone and thus the term “myofascial pain” was applied.

Her next idea was that the myofascial trigger area was a focus of a self-sustaining cycle of noxious afferent nerve impulses between the CNS and periphery and that muscles could indefinitely maintain themselves in a state of hypertonicity. Her EMG studies suggested that the trigger area was a high-frequency electrically discharging focus. She used the terms “myofascial trigger areas” and “somatic trigger areas” interchangeably.

Military surgeons and others at that time had reported success with local anaesthetic injections of fibrous connective tissue of sprained joints. Likewise she found that treating patients with acute ankle and knee sprains who had trigger areas in joint capsules, ligaments and adjacent musculo-tendinous junctions also reported relief but instead of widely infiltrating the procaine she aimed her needle at identifiable exquisitely tender spots in the sprain. Following that she found that normal saline and dry needling achieved the same results. She determined however that the use of local anaesthetic would reduce the pain of the treatment and enhance not only the comfort of the patient but also the efficacy of the injection. The local anaesthetic seemed to block the neuromuscular junction as well as sensory afferents and to decrease or abort

the high-frequency discharges that were maintaining the clinical picture.

In 1946 in the cardiac ward, she introduced arm exercises and early chair rest rather than bed rest in the post-infarction phase of treatment, reducing the incidence of painful stiff shoulder and arm. She deduced that the aetiology of this condition was at least in part mechanical and not entirely due to “psychogenic rheumatism”. She concluded that much painful disability, thought to be osteoarthritis, was in fact mediated by latent trigger mechanisms in associated skeletal muscles and that local therapy should be applied to active or latent trigger areas rather than loci of referred pain.

In the early 1950s, she became interested in using vapocoolant sprays, firstly ethyl chloride then the safer fluoromethane spray. Through this she became involved with the US and Canadian Armed Services in the research on “cold injury” which took her to the sub Arctic Circle. There she discovered that repeated exposure to heat or cold conferred tissue protection to subsequent exposure similar to her observations that repeated brief cold exposure to vapocoolant spray reduced perception of cold in that area for a period afterwards.

She considered that pain and temperature sensations probably shared the same neural

pathways and that vapocoolant spray enabled blocking of afferent nociception from trigger areas. Experimentation with temperature sensing instruments indicated the mechanism of action was probably neurogenic, rather than refrigeration anaesthesia of nerve fibres, and that the vapocoolant spray did not change the temperature of deeper muscle tissues.

With growing recognition of her success at treating musculoskeletal pain she was called to assist Senator John Kennedy who had severe back pain following injuries sustained in WW2. When Kennedy became US President in 1960 she was appointed his personal physician. One of her treatments for the new president was to use a rocking chair, which then became a popular American household furniture item. She continued in the White House under Lyndon Johnson but retired part way through his administration when she was in her mid-sixties. She continued working until her death in her nineties.

Whilst David Simons was not mentioned in her autobiography, it is quite possible that she met him during lectures at various air force and space medicine establishments. Apparently it was he who wrote the text of most of the three volumes of *Myofascial Pain and Dysfunction*.<sup>6</sup>

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## See also:

Travell J. *Office hours: day and night: The autobiography of Janet Travell M, NAL*. New York: World Publishing Company, 1968.

# Book review

**Book title:** *Emergencies in Sports Medicine*

**Editor:** Dr Julian Redhead and Dr Jonathon Gordon

**Publication information:** Oxford University Press, Oxford, UK. 2012.

**Availability:** Available from Oxford University Press or Amazon for around \$47.95 plus shipping

**Reviewed by:** Dr Scott Masters

This 336-page pocket-size book is “a concise guide to the practical management of sporting emergencies” as described by the authors.

It consists of 22 chapters covering a wide range of topics including information on the standard areas of collapse, spinal injuries, trauma and general emergencies.

Sections on paediatrics, athletes with disability, aggressive patients and breaking bad news round out the handbook nicely and add value to the core chapters.

The book is set out in an easy-to-read format. There are reference headings at the start of each chapter.

Subheadings are clearly marked, with most information in dot point or table form. The section on head injuries, for example, has been broken into:

- Pitchside equipment and preparation
- Pitchside assessment
- Minor head injury
- Significant head injury
- Concussion
- Subdural
- Extradural

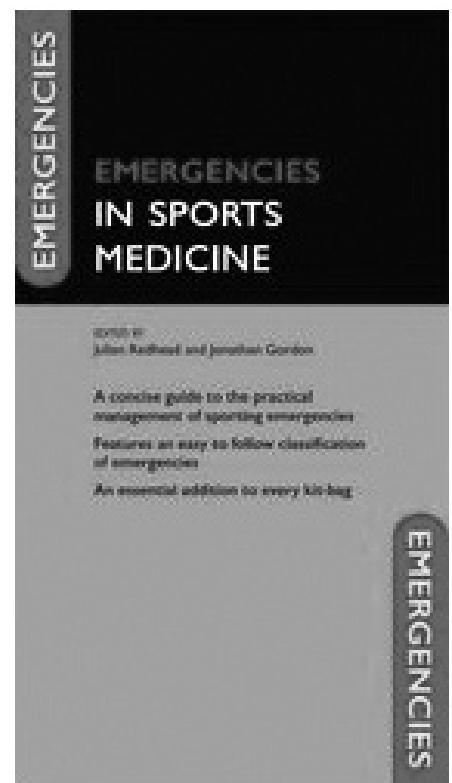
- Diffuse cerebral swelling
- Intracerebral haematoma
- Scalp injuries.

It has quite comprehensive coverage with practical up-to-date recommendations. Useful tips are throughout the book, such as the recommendations on facial injuries, i.e., “document all missing teeth and their whereabouts – if necessary you will need to make sure they are not in the airway (chest X-ray)”.

This book would most suit doctors who provide medical care at sporting events. It has quite comprehensive emergency management notes for conditions likely to be seen acutely at competition or training events and is a handy size for transport.

It would also be useful for sports medicine practitioners in general as there is concise information on prevention in some areas, advice for athletes with pre-existing conditions and tips regarding communicating with the media and other sports bodies.

I give it a 3-star AAMM rating.





# Book review

**Book title:** *Oxford Handbook of Sport and Exercise Medicine*, 2nd edition

**Editor:** Domhnall MacAuley

**Publication information:** Oxford University Press, Oxford, UK. 2013. 755 pp. ISBN 9780199660155, softcover.

**Availability:** New on Amazon for \$39 – \$60 and used for \$22 plus shipping charges. Also available as a eBook.

**Reviewed by:** Christine Brooks. Griffith University School of Rehabilitation Sciences and Coaching Science Education Coordinator for USA Track and Field.

The resource is designed as a pocket-sized (180 x 100 mm) desk reference and covers the curriculum for postgraduate sport and exercise medicine exams in the UK. It would also serve as a valuable quick reference in emergency situations for general practitioners, team doctors, university doctors and other specialists working in sport and exercise medicine (including physiotherapy and rehabilitation practitioners).

The second edition is partitioned into 25 topics each written by 28 leaders in academic sport and exercise medicine, 18 of whom are drawn from the United Kingdom and Ireland and 10 from Australia (2), Italy (3), USA (1), Canada (3) and South Africa (1).

The editor, Domhnall MacAuley, has specialist accreditation in sports and exercise medicine and has held various editorial roles with the *British Medical Journal* in addition to serving as editor-in-chief of the *British Journal of Sports Medicine*. He has played a leadership role in establishing sports medicine as an academic specialty in the United Kingdom.

The handbook collates recommendations for optimal treatment, preventive strategies and evidence-based protocols in sports and exercise medicine.

The topics include 1. Immediate care, 2. Sports injury, 3. Physiotherapy and rehabilitation, 4. Benefits of exercise, 5. Exercise physiology, 6. Metabolic, 7. Aids to performance, 8. Disability, 9. Arthritis, 10. Cardiorespiratory, 11. Infectious disease, 12. Dermatology, 13. Women, 14. Older people, 15. Head and face, 16. Spine, 17. Shoulder, 18. Elbow and forearm, 19. Wrist and hand, 20. Abdomen, 21. Hips and pelvis, 22. Knee, 23. Ankle and lower leg,

24. Foot, 25. The team physician.

The information on each topic is presented in an efficient bullet-point format. The print is quite small, so the amount of information covered substantial given the size of the handbook.

Topics 15-24 focus in large part on the management of sports injuries. Topic 13 addresses women's issues, beginning with a brief overview of the menstrual cycle and then focuses on the outlining the key irregularities frequently occurring in female athletes such as exercise-induced menstrual irregularities and treatment and an extensive two-page discussion of the female triad (amenorrhoea, eating disorder and osteoporosis or osteopenia).

The 24 pages outline the benefits of exercise, summarising what is currently known about health and physical activity, determinants of physical activity, behavioral change, intervention programs and the overweight and obesity issue among children.

Most sports medicine specialists will likely be familiar with most of the information contained in this section. However, the following topic on exercise physiology (44 pages) will likely contain unfamiliar information and therefore provide valuable insights for the general practitioner treating the recreational athlete.

Topic 10 includes 40 pages overviewing a wide array of issues related to coronary artery disease, cardiac rehabilitation, exercise in adult congenital heart disease, exercise testing and the effects of exercise in heart failure among other cardiorespiratory health issues. This section will be useful for practitioners wanting a quick overview of current knowledge, exercise treatment and



management of cardiorespiratory diseases.

Topic 6 entitled “Metabolic” addresses a broad variety of issues including nutritional requirements, recovery after exercise, impact of the environment and overtraining syndrome. The issue of overtraining is becoming a serious health problem among team sport athletes and the symptoms are often unfamiliar to many sports and medicine practitioners.

Overall, the handbook is well conceived and thoroughly prepared. There is also an American version of the handbook that basically includes the same topics but has been reworded slightly.

# Journal abstracts

*The following is a selection of abstracts which you might find relevant to your practice. The opinions of the reviewers are their own.*

**Vetrano M, Castorina A, Vulpiani MC, Baldini R, Pavan A, Ferretti A. Platelet-Rich Plasma Versus Focused Shock Waves in the Treatment of Jumper's Knee in Athletes. *Am J Sports Med* 2013;41(4):795-803.**

**Background:** Tendinopathies represent a serious challenge for orthopaedic surgeons involved in treatment of athletes.

**Purpose:** To compare the effectiveness and safety of platelet-rich plasma (PRP) injections and focused extracorporeal shock wave therapy (ESWT) in athletes with jumper's knee.

**Study Design:** Randomized controlled trial; Level of evidence, 1.

**Methods:** Forty-six consecutive athletes with jumper's knee were selected for this study and randomized into 2 treatment groups: 2 autologous PRP injections over 2 weeks under ultrasound guidance (PRP group;  $n = 23$ ), and 3 sessions of focused extracorporeal shock wave therapy (2400 impulses at 0.17-0.25 mJ/mm, 2 per session) (ESWT group;  $n = 23$ ). The outcome measures were Victorian Institute of Sports Assessment-Patella (VISA-P) questionnaire, pain visual analog scale (VAS), and modified Blazina scale. A reviewer who was blinded as to the group allocation of participants performed outcome assessments before treatment and at 2, 6, and 12 months after treatment. Nonparametric tests were used for within-group (Friedman/Wilcoxon test) and between-group (Kruskal-Wallis/Fisher test) testing, and the significance level was set at .05.

**Results:** The 2 groups were homogeneous in terms of age, sex, level of sports participation, and pretreatment clinical status. Patients in both groups showed statistically significant improvement of symptoms at all follow-up assessments. The VISA-P, VAS, and modified Blazina scale scores showed no significant differences between groups at 2-month follow-up ( $P = .635$ ,  $.360$ , and  $.339$ , respectively). The PRP group showed significantly better improvement than the ESWT group in VISA-P, VAS scores at 6- and 12-month follow-up, and modified Blazina scale score at 12-month follow-up ( $P < .05$  for all).

**Conclusion:** Therapeutic injections

of PRP lead to better midterm clinical results compared with focused ESWT in the treatment of jumper's knee in athletes.

**Comment:** Patellar tendinopathy principally affects the attachment of the patellar tendon to the inferior pole of the patella in athletes whose sport involves repeated jumping.

It is often chronic and resistant to exercise-based treatments. Increasing interest in PRP injections prompted this pragmatic randomised controlled trial comparing it with extracorporeal shock wave therapy.

Both treatments claim to work by releasing growth factors that promote tendon healing. The study, involving 46 competitive athletes, was well conducted with complete followup.

Both treatments were supplemented by the same stretching and isotonic/isometric strengthening regime. Both treatment groups showed clinically significant improvements in the VISA-P scores and pain scores after 2 months but after this the ESWT group plateaued while the PRP group continued to improve.

At the 6-month mark, despite a rather modest sample size, clinically significant greater improvements in VISA-P scores, pain scores, satisfaction and return to full sporting activities were noted in the PRP group compared with the ESWT group.

The gap between the groups widened at 12 months. One problem in generalising the results of this study is the lack of standardised treatment protocols for both therapies, although the paper gives enough detail for the reader to perform the therapies as described.

The study does not address the mechanism of action of PRP, a treatment that shares in common microtrauma to tendon fibres, neovessels and small nerves inherent in other injection therapies for tendinopathies.

— Assoc Prof Michael Yelland

**Ikeda DM, McGill SM. Can altering motions, postures, and loads provide immediate low back pain relief: a study of 4 cases investigating spine load, posture, and stability. *Spine* (Phila Pa**

**1976) 2012;37(23).**

**Study design:** A quantitative biomechanical analysis of mechanism of pain alteration in 4 cases of low back pain.

**Objective:** To investigate the contributions of a number of biomechanical factors associated with pain alteration.

**Summary of background data:** Some clinicians use mechanically based manual interventions in attempt to reduce low back pain. However, the mechanism of pain alteration remains unknown.

**Methods:** A sample was formed with 4 patients with low back pain seeking consults for pain relief. All could produce "catches" of pain with movement. Manual interventions involving coached changes in motion and muscle activation attempted to reduce pain. Electromyographic and kinematic data were collected before and after intervention. These data were input to an anatomically detailed spine model that calculated muscle force, joint compression and shear, and spine stability.

**Results:** Using a clinically significant criterion of pain reduction of two or more, three of four subjects reduced pain immediately upon the intervention. Using a change of 10% as a criterion for biological significance for kinematic and kinetic variables, each subject demonstrated a different reaction. For example, subject 1 demonstrated increased stability, subject 2 increased mediolateral shear, subject 3 increased mediolateral shear and decreased spine flexion, and subject 4 increased stability. The pain-reducing interventions required to obtain these results were also different for each individual.

**Conclusion:** Immediate pain reduction can be achieved by altering muscle-activation and movement patterns. However, the combination for optimal success seems to be different for every individual. Pain provocation tests help to "tune" the intervention. This also suggests that patient-classification schemes may need more refinement to address this heterogeneity.

**Comment:** This small series of cases is co-authored by McGill, a kinesiologist and director of a spinal biomechanics laboratory in Canada, whose focus has been on the

detailed assessment of biomechanical abnormalities underlying pain and the use of exercise to compensate for these. It acts as a reminder that one size does not fit all in so-called “non-specific low back pain”.

Each patient showed very different biomechanical responses to loading, flexion, extension and tasks such as squatting, jumping and sitting down.

On the basis of clinical assessment they were labelled as intolerant of certain movements and postures and, not surprisingly, different interventions were successful at reducing their instantaneous pain such as abdominal bracing, a “latissimus dorsi intervention” and bending with the hips rather than with the spine.

This is reminiscent of other research showing that tailored exercises are more effective than standardised exercises in the management of low back pain.

It reminds us to consider the finer points of history and examination before giving advice about posture and specific exercises and not just use one or two recipes for all low back pain patients. - Assoc Prof Michael Yelland

**Manchikanti L, Singh V, Cash KA, Pampati V.J. Assessment of effectiveness of percutaneous adhesiolysis and caudal epidural injections in managing post lumbar surgery syndrome: 2-year follow-up of a randomized, controlled trial. *Pain Res* 2012;5:597-608.**

Full article available <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3533727/>

**Background:** The literature is replete with evaluations of failed surgery, illustrating a 9.5-25% re-operation rate. Speculated causes of post lumbar surgery syndrome include epidural fibrosis, acquired stenosis, recurrent disc herniation, sacroiliac joint pain, and facet, joint pain among other causes.

**Methods:** Patients (n = 120) were randomly assigned to two groups with a 2-year follow-up. Group I (control group, n = 60) received caudal epidural injections with catheterization up to S3 with local anesthetic (lidocaine 2%, 5 mL), nonparticulate betamethasone (6 mg, 1 mL), and 6 mL of 0.9% sodium chloride solution. Group II (intervention group, n = 60) received percutaneous adhesiolysis of the targeted area, with targeted delivery of lidocaine 2% (5 mL), 10% hypertonic sodium chloride solution (6 mL), and nonparticulate betamethasone (6 mg). The multiple outcome measures included the Numeric Rating Scale, the Oswestry Disability Index 2.0, employment status, and opioid intake with assessments

at 3, 6, 12, 18, and 24 months post treatment. Primary outcome was defined as 50% improvement in pain and Oswestry Disability Index scores.

**Results:** Significant improvement with at least 50% relief with pain and improvement in functional status was illustrated in 82% of patients at the 2-year follow-up in the intervention group compared to 5% in the control group receiving caudal epidural injections. The average number of procedures over a period of 2 years in Group II was  $6.4 \pm 2.35$  with overall total relief of approximately 78 weeks out of 104 weeks.

**Conclusion:** The results of this study show significant improvement in 82% of patients over a period of 2 years with an average of six to seven procedures of 1-day percutaneous adhesiolysis in patients with failed back surgery syndrome.

**Comment:** The management of patients with persistent pain following spinal surgery is difficult, with considerable uncertainty as to the aetiology of the pain. Repeat MRI sometimes reports perineural fibrosis/adhesions or similar and the problem then is what treatment, apart from analgesia, can be offered to the patient.

This report from Manchikanti indicates that percutaneous adhesiolysis may well be a useful option compared to the control of a caudal epidural.

The radiology provider that I use in Brisbane has performed this on one of my patients with persistent pain post micro-discectomy. Whilst there was some benefit the patient still continues to require regular analgesia. She has not however had repeat of the procedure., whereas this paper indicates considerably more than one treatment is required.

Whilst there was some benefit the patient still continues to require regular analgesia. She has not however had repeat of the procedure, whereas this paper indicates considerably more than one treatment is required.

This is potentially a valuable technique to consider in cases where scarring or adhesions are present and will it probably be more readily accessible than epiduroscopy.

- Dr Tom Baster

**Moon HJ, Choi KH, Kim DH et al. Effect of lumbar stabilization and dynamic lumbar strengthening exercises in patients with chronic low back pain. *Ann Rehabil Med* 2013 Feb;37(1):110-7.**

Full article available: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3604220/>

**Objective:** To compare the effects of

lumbar stabilization exercises and lumbar dynamic strengthening exercises on the maximal isometric strength of the lumbar extensors, pain severity and functional disability in patients with chronic low back pain (LBP).

**Methods:** Patients suffering nonspecific LBP for more than 3 months were included prospectively and randomized into lumbar stabilization exercise group (n=11) or lumbar dynamic strengthening exercise group (n=10). Exercises were performed for 1 hour, twice weekly, for 8 weeks. The strength of the lumbar extensors was measured at various angles ranging from 0° to 72° at intervals of 12°, using a MedX. The visual analog scale (VAS) and the Oswestry Low Back Pain Disability Questionnaire (ODQ) were used to measure the severity of LBP and functional disability before and after the exercise.

**Results:** Compared with the baseline, lumbar extension strength at all angles improved significantly in both groups after 8 weeks. The improvements were significantly greater in the lumbar stabilization exercise group at 0° and 12° of lumbar flexion. VAS decreased significantly after treatment; however, the changes were not significantly different between the groups. ODQ scores improved significantly in the stabilization exercise group only.

**Conclusion:** Both lumbar stabilization and dynamic strengthening exercise strengthened the lumbar extensors and reduced LBP. However, the lumbar stabilization exercise was more effective in lumbar extensor strengthening and functional improvement in patients with nonspecific chronic LBP.

**Comment:** This study contributes little to the debate on the value of lumbar exercises for chronic lumbar spinal pain. There are few patients in each group (10 and 11) and the lack of a specific diagnosis makes the study difficult to assess. For example, are strengthening exercises useful for zygoapophysial cases and not useful for discogenic lumbar spinal pain or vice versa?

Clinically my impression is that flexion exercises are useful for the former and extension better for the latter and “at the coalface” the patient will usually be able to report which sort of exercise seems to help relieve their pain.

In that regard, I find the simple exercises described by Professor Nik Bogduk and Dr Brian McGuirk in *Australasian Musculoskeletal Medicine* 2008 May 13(1) 8-14 useful. However it is important to keep reassessing the value of different types of exercises for chronic spinal pain and it at least provides the patient with a level of self management and involvement.



This study indicates that only one hour twice a week of lumbar extension or stabilisation exercises can reduce pain and disability. - *Dr Tom Baster*

**Wang Y, Videman T, Battié M. SSLS prize winner: Lumbar vertebral endplate lesions: associations with disc degeneration and back pain history. *Spine* (Phila Pa 1976). 2012 Aug 1;37(17):1490-6.**

*Study design:* An autopsy study.

*Objective:* To investigate associations between various types of lumbar endplate lesions, disc degeneration (DD), and back pain history.

*Summary of background data:* The well-innervated vertebral endplate has been suspected as a source of back pain. Previously, we observed 4 types of lumbar endplate lesions with distinct morphological characteristics. Their roles in DD and back pain remain unclear.

*Methods:* From a lumbar spine archive of 136 men (mean age, 52 yr), back pain, back injury, and occupation history data for 69 subjects and discography data for 443 discs from 109 subjects were available for study. Back pain history was categorized as none, occasional, or frequent. DD was judged from discography. Endplate lesions were classified as Schmorl's nodes, fracture, erosion, or calcification, and lesion size was rated as none, small, moderate, or large. Associations between endplate lesions and DD, back pain history, back injury, and occupation history were examined.

*Results:* Presence of endplate lesions was associated with frequent (odds ratio [OR] = 2.57) but not occasional back pain. However, large endplate lesions were associated with both occasional (OR = 8.68) and frequent (OR = 17.88) back pain. This association remained after further controlling for DD. Also, the presence of each type of endplate lesion was associated with adjacent DD (OR = 2.40-9.71), with larger lesions associated with more severe DD. Endplate erosion lesions were more strongly associated with adjacent DD than Schmorl's nodes. Although back injury history was associated with the presence of fracture and erosion lesions, heavy occupation was associated with the presence of Schmorl's nodes.

*Conclusion:* Endplate lesions are associated with back pain as well as being closely associated with adjacent DD, with a clear dosage effect. Different types of endplate lesions seem to have different magnitudes of associations with DD. Lumbar endplate lesions may be an important key to better understand both

DD and back pain.

**Comment:** This autopsy-based study tries to correlate abnormal vertebral endplate findings, disc degeneration and back pain.

The history of back pain was collected via telephone interview of living relatives of the specimens studied and thus is possibly prone to some reporting errors. Where actually is the pain arising in chronic discogenic back pain is a relevant issue. The vertebral endplates are well innervated and, akin to knee and hip arthritis, is the pain arising at the cortical/subcortical bony levels rather than the degenerative disc? Provocative discography is often used and does replicate patient pain and a recent "null hypothesis" essay<sup>1</sup> that discs do not cause back pain was also not able to be sustained.

The study reports good odds ratios for the association of endplate lesions and adjacent disc degeneration which on reflection is not really surprising. However there also seems to be an underlying association of back pain with endplate lesions with an odds ratio of 5.5 (CI 1.15-26.23) between the findings of calcification at the endplate and frequent back pain. - *Dr Tom Baster*

1. Bogduk N, Aprill C, Derby R. Lumbar Discogenic Pain: State-of-the-Art Review. *Pain Med* 2013 Apr 8.

**Penny P, Geere J, Smith T. A systematic review investigating the efficacy of laterally wedged insoles for medial knee osteoarthritis. *Rheumatol Int* 2013 Apr 24.**

A conservative management strategy for knee osteoarthritis is the lateral wedge insole (LWI). The theoretical basis for this intervention is to correct tibiofemoral malalignment, thereby reducing pain and optimising function.

This systematic review evaluates the evidence on the effectiveness and safety of LWI for the treatment for knee osteoarthritis. A systematic review was performed, searching published (MEDLINE, AMED, EMBASE, CINAHL, Cochrane Library) and unpublished literature from their inception to August 2012. Randomised controlled trials (RCTs) were

included that compared the use of LWI with a neutral insole or control intervention for people with medial compartment osteoarthritis.

Risk of bias and clinical relevance were assessed, and outcomes were analysed through meta-analysis. From a total of 3,105 citations, 10 studies adhered to the a priori eligibility criteria. These included 1,095 people; 535 participants were allocated to receive LWI insoles compared to 509 in control groups. Eight per cent of papers

were of high quality with low risk of bias.

There was no statistically significant difference between LWI and neutral insoles for pain, function, analgesic requirement, compliance or complications ( $p \geq 0.07$ ). Those who received LWI demonstrated lower non-steroidal anti-inflammatory drug requirements ( $p < 0.001$ ).

To conclude, there is limited evidence to support the prescription of LWI to people with medial compartment osteoarthritis to reduce pain and increase function. However, there remains a paucity of evidence to determine whether LWI outcomes differ in subgroups of the patients, such as severe compared to mild osteoarthritis, obese patients, or whether the angle of LWI is of clinical importance.

**Comment:** Patients with knee osteoarthritis often present with a varus (or "bow legged") deformity. This is associated with about a four-fold increase in the odds of progression of the disease compared to knees with normal alignment over the relatively short period of 18 months.<sup>1</sup>

A fairly standard treatment used for such cases has been the use of unloading braces (probably not effective however) or realignment via a tibial osteotomy, as an alternative to a knee replacement especially in younger patients.

However a simpler option often suggested by our allied health colleagues is in-shoe wedges - are they effective?

It is tempting to think theoretically they could help but this systematic review seems to indicate probably not, with the proviso that maybe subgroups may benefit. - *Dr Tom Baster*

1. Sharma L, Song J, Felson DT et al. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. *JAMA* 2001 Jul 11;286(2):188-95.

**Bellato E, Marini E, Castoldi F, et al. Fibromyalgia syndrome: etiology, pathogenesis, diagnosis, and treatment. *Pain Res Treat* 2012;2012:426130.**

Full article available: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3503476/>

Fibromyalgia syndrome is mainly characterized by pain, fatigue, and sleep disruption. The etiology of fibromyalgia is still unclear: if central sensitization is considered to be the main mechanism involved, then many other factors, genetic, immunological, and hormonal, may play an important role.

The diagnosis is typically clinical (there are no laboratory abnormalities) and the physician must concentrate on pain and on its features. Additional symptoms (e.g.,

Raynaud's phenomenon, irritable bowel disease, and heat and cold intolerance) can be associated with this condition.

A careful differential diagnosis is mandatory: fibromyalgia is not a diagnosis of exclusion. Since 1990, diagnosis has been principally based on the two major diagnostic criteria defined by the ACR. Recently, new criteria have been proposed.

The main goals of the treatment are to alleviate pain, increase restorative sleep, and improve physical function. A multidisciplinary approach is optimal.

While most nonsteroidal anti-inflammatory drugs and opioids have limited benefit, an important role is played by antidepressants and neuromodulating antiepileptics: currently duloxetine (NNT for a 30% pain reduction 7.2), milnacipran (NNT 19), and pregabalin (NNT 8.6) are the only drugs approved by the US Food and Drug Administration for the treatment of fibromyalgia. In addition, nonpharmacological treatments should be associated with drug therapy.

**Comment:** This article gives a good overview of current thinking on fibromyalgia, with central sensitisation still considered the main mechanism. It provides details on the clinical diagnosis which now places less emphasis on the symmetrical tender points traditionally used.

With the recent approval of pregabalin in Australia for neuropathic pain it will be interesting clinically to observe the response in patients with fibromyalgia symptoms associated with an underlying neuropathic diagnosis. Indeed some physicians are of the opinion that fibromyalgia is a neuropathic disorder, although this is not generally accepted.<sup>1</sup> – *Dr Tom Baster*

1. Rowbotham M. Is fibromyalgia a neuropathic pain syndrome? *Rheumatol Suppl* 2005 Aug;75:38-40.

**MacVicar J, King W, Landers MH, Bogduk N. The effectiveness of lumbar transforaminal injection of steroids: a comprehensive review with systematic analysis of the published data. *Pain Med* 2013 Jan;14(1):14-28.**

**Objective:** To determine the effectiveness of lumbar transforaminal injection of steroids in the treatment of radicular pain.

**Design:** Comprehensive review of the literature with systematic analysis of all published data.

**Interventions:** Four reviewers independently assessed 39 publications on the effectiveness of lumbar transforaminal injection of steroids. Each reviewer determined if a publication provided

any valid information on effectiveness. Assessments were compared, and the data of each publication were evaluated in terms of the rigor with which they were produced and the evidence they provided of effectiveness.

**Outcome measures:** The primary outcome sought was the success rate for relief of pain. Improvement in secondary outcomes was noted if reported.

**Results:** For miscellaneous conditions, the available evidence is limited and is neither compelling nor conclusive. For disc herniation, the evidence is sufficiently abundant to show that lumbar transforaminal injection of steroids is not universally effective but, nevertheless, benefits a substantial proportion of patients, and is not a placebo. Success rates are higher in patients with contained herniations that cause only low-grade compression of the nerve.

**Conclusion:** In a substantial proportion of patients with lumbar radicular pain caused by contained disc herniations, lumbar transforaminal injection of corticosteroids is effective in reducing pain, restoring function, reducing the need for other health care, and avoiding surgery. The evidence supporting this conclusion was revealed by comprehensive review of all published data and found to be much more compelling than it would have been if the literature review had been of the limited scope of a traditional "systematic review" of randomized, controlled trials only.

**Comment:** It is reassuring to have one's clinical impressions for procedures and interventions one utilises in clinical practice supported by reports such as this in the literature. It is also reassuring that the procedures are inherently of low risk, which does not imply "no risk".

The authors point out that the only potentially catastrophic complication of the procedure is spinal cord infarction due to inadvertent injection of particulate steroids into the spinal artery, of which there have been eight cases reported in the literature. However this can be avoided if very strict injection protocols are adhered to.

What does not come to light in this abstract, but which this review reports, is that TFIs are only slightly less efficacious in chronic versus acute radicular pain states. They also looked into the effectiveness of TFIs in cases of spinal stenosis.

While 50% of people seemed to achieve 50% relief lasting six months or more, they pointed out that rigorous studies for this clinical entity are lacking.

They also found that the literature for the use of TFIs in failed back surgery

syndrome and epidural lipomatosis is seriously lacking.

The former has been addressed in a subsequent article<sup>1</sup> where it was found that for TFIs in people with persistent symptoms after surgery, only about 27% of patients achieved 50% of pain relief, for periods ranging from 4 to 34 months (mean 15.5 months).

Interestingly, the procedure was more effective in those without recurrent disc herniation. These facts should be taken into account when discussing the potential use of TFIs with patients, before embarking on these interventions. – *Dr Steve Jensen*

1. Klessinger S. Radicular pain in post lumbar surgery syndrome: the significance of transforaminal injection of steroids. *Pain Med* 2013;14:243-246.

**Holliday S, Magin P, Dunbabin J et al An evaluation of the prescription of opioids for chronic nonmalignant pain by Australian general practitioners. *Pain Med* 2013;14(1):62-74.**

**Objective:** Our objective was to evaluate the quality of opioid analgesia prescribing in chronic nonmalignant pain (CNMP) by general practitioners (GPs, family physicians).

**Design:** An anonymous, cross-sectional questionnaire-based survey.

**Setting:** The setting was five Australian divisions of general practice (geographically based associations of GPs).

**Methods:** A questionnaire was mailed to all division members. Outcome measures were adherence to individual recommendations of locally derived CNMP practice guidelines.

**Results:** We received 404 responses (response rate 23.3%). In the previous fortnight, GPs prescribed long-term continuous opioids for CNMP for a median of 4 and a mean of 7.1 ( $\pm 8.7$ ) patients with CNMP. Guideline concordance (GLC) was poor, with no GP always compliant with all guideline items, and only 31% GPs usually employing most items. GLC was highest for the avoidance of high dosages or fast-acting formulations. It was lowest for strategies minimising individual and public health harms, such as the initiation of opioids on a time-limited trial basis, use of contracts, and the preclusion or management of aberrant behaviours. GLC was positively associated with relevant training or qualifications, registration with the Australian Prescription Drug Monitoring Programme, being an opioid substitution therapy prescriber, and female gender.

**Conclusions:** In this study, long-term opioids were frequently initiated for CNMP without a quality use-of-medicine approach. Potential sequelae are inadequate

treatment of pain and escalating opioid-related harms. These data suggest a need for improved resourcing and training in opioid management across pain and addictions.

**Comment:** The authors looked at the adherence by GPs to locally derived chronic nonmalignant pain (CNMP) practice guidelines.

It highlights the fact that it is one thing to devise practice guidelines, but implementing them into widespread clinical practice proves to be very difficult.

The authors point out that their anonymous cross-sectional questionnaire-based survey attracted the poor response rate of only 23.3% of GPs surveyed, but claim that this is similar to other GP surveys.

A number of potential reasons for poor compliance to the CNMP practice guidelines are proposed:

- GPs practising streamlined medicine may be unwilling or unable to target Guideline Concordance (GLC)
- Pain presentations are often associated with co-morbidities lacking simple solutions, *with GPs time poor, and grossly under remunerated to deal with them adequately* (– my emphasis).
- GPs may feel that GLC is ineffective, and so unnecessary.
- They may prioritise the doctor-patient relationship and fear losing a patient angry or frustrated due to a structured policy on refill scripts.
- There may be a perceived loss of control over the prescription process, or a clinical inertia to continue chronic opioid therapy (COT) prescribed by colleagues over decades.
- Pharmaceutical industry education may encourage a permissive approach to prescription opioids (POs) or leave GPs unaware of prescription guidelines.
- Structural reasons may account for low GLC, such as underfunding causing long waiting lists for multidisciplinary pain services or addiction services.
- *For an already overburdened GP to prioritise the time and diligence involved in more responsible prescription, specific reimbursement will be required* (– again my emphasis).

As we are constantly reminded, CNMP is becoming an increasing social and economic burden on all Western societies.

Managing such pain requires a multimodal approach, of which prescription opioids may be, but are not always, a necessary part.

The primary care physician is an integral part, and probably the most important cog, in the health care machinery to deal with this complex issue.

As implied by this article, at present GPs do not have the financial incentive to set aside the considerable time and effort to adequately manage such patients. Therefore healthcare policy makers and governments need to find a way to adequately reimburse practitioners with the clinical competency and willingness to devote this time.

I dare say the vast majority, if not all, AAMM and NZAMM members would fall into this category. – *Dr Steve Jensen*

**Chen L, Zhang J, Li F et al. Endogenous anandamide and cannabinoid receptor-2 contribute to electroacupuncture analgesia in rats. J Pain. 2009 Jul;10(7):732-9.**

Acupuncture is widely used clinically to treat acute and chronic pain conditions, but the mechanisms underlying its effect are not fully understood. Although endocannabinoids are involved in modulation of nociception in animal models and in humans, their role in acupuncture analgesia has not been assessed. In this report, we determined the effect of electroacupuncture (EA) on the level of anandamide in the skin tissue and the role of cannabinoid CB1 and CB2 receptors in the analgesic effect of EA in an animal model of inflammatory pain.

Inflammatory pain was induced by local injection of complete Freund's adjuvant (CFA) into the hind paw of rats. Thermal hyperalgesia was tested with a radiant heat stimulus, and mechanical allodynia was quantified with von Frey filaments. The anandamide concentration in the skin tissue was measured by using high-performance liquid chromatography. EA, applied to GB30 and GB34, at 2 and 100Hz significantly reduced thermal hyperalgesia and mechanical allodynia induced by CFA injection.

Compared with the sham group, EA significantly increased the anandamide level in the inflamed skin tissue. Local pretreatment with a specific CB2 receptor antagonist, AM630, significantly attenuated the antinociceptive effect of EA. However, the effect of EA was not significantly altered by AM251, a selective CB1 receptor antagonist.

These findings suggest that EA potentiates the local release of endogenous anandamide from inflamed tissues. Activation of peripheral CB2 receptors contributes to the analgesic effect of EA on inflammatory pain.

**Perspective:** This study shows

that electroacupuncture increases the anandamide level in inflammatory skin tissues, and CB2 receptors contribute to the analgesic effect of electroacupuncture in a rat model of inflammatory pain. This information improves our understanding of the mechanisms involved in the analgesic effect of acupuncture.

**Comment:** There is compelling evidence for the scientific basis of acupuncture analgesia. Recent review articles<sup>1,2,3</sup> are comprehensive in their coverage of the topic. The majority of research on acupuncture analgesia has focused on neural pathways including afferent nerve fibres, ascending/descending spinal pathways, neurotransmitters, neuromodulators and functional imaging. In particular, the role of opioid peptides has been extensively investigated.

There has been very little attention given to the role of the endocannabinoid system in acupuncture analgesia.

This study compared the effects of electro-acupuncture and sham electro-acupuncture in a rat model of inflammatory pain. It demonstrated that:

- Electro-acupuncture reduced thermal hyperalgesia and mechanical allodynia but sham electro-acupuncture did not.
- Electro-acupuncture increased the level of endogenously released anandamide in inflamed skin tissue but sham electro-acupuncture did not.

By using selective cannabinoid receptor (CB1 and CB2) antagonists, this study also examined the roles of CB1 and CB2 receptors in acupuncture analgesia. It demonstrated that:

- A CB2 receptor antagonist attenuated the anti-nociceptive effect of electro-acupuncture.
- A CB1 receptor antagonist did not attenuate the anti-nociceptive effect of electro-acupuncture.

The article concludes that the endocannabinoid system plays a role in acupuncture analgesia when electro-acupuncture is deployed.

This provides another possible mechanism for acupuncture analgesia, one that involves the release of endogenous anandamide with action on the CB2 receptors. – *Dr Thomas Choong*

1. Han JS. Acupuncture analgesia: Areas of consensus and controversy. *Pain* 2011; 152: S41-S48.

2. Wang SM, Kain ZN, White P. Acupuncture Analgesia: I. The Scientific Basis. *Anesthesia and Analgesia* 2008; 106(2): 602-10.

3. Zhao ZQ. Neural mechanism underlying acupuncture analgesia. *Progress in Neurobiol* 2008; 85: 355-375.



# Educational Activities

## Masters, Diploma, and Certificate Courses in Musculoskeletal Medicine Flinders University Diploma/Certificate in Musculoskeletal Medicine

Date	Title/Key Resource Person	Venue	Provider	Contact	CME Points
2013	Graduate Diploma in Musculoskeletal Medicine	Flinders Medical Centre	School of Health Sciences, Bedford Park SA 5042	Mr Don Bramwell, Ph +61 8 8204 4673; <a href="mailto:donald.bramwell@flinders.edu.au">donald.bramwell@flinders.edu.au</a>	TBA

## University of Otago Diploma/Certificate in Musculoskeletal Medicine, Masters/Diploma/Certificate in Health Sciences (Pain and Pain Management)

Date	Title/Key Resource Person	Venue	Provider	Contact	CME Points
2013	<i>On campus papers</i> Clinical Diagnosis Part 1 Clinical Therapeutics Clinical Diagnosis Part 2  <i>Distance taught papers</i> Pain Pain Management Regional Disorders (Spine) Regional Disorders (Limbs) MSM Rehabilitation Recreational and Sports Injuries Pain Assessment Neurobiology of Pain Biomedical Aspects of Pain Psychosocial and Cultural Aspects of Pain	On-campus course University of Otago, Christchurch  Distance taught papers - fortnightly audioconferences ex University of Otago, Christchurch	University of Otago	Enrolments: Veronica McGroggan Ph +64 3 364 1086 Fax +64 3 364 0909 <a href="mailto:veronica.mcgroggan@otago.ac.nz">veronica.mcgroggan@otago.ac.nz</a> or Geoff Harding Ph +61 7 3269 5522 Fax +61 7 3269 6407 <a href="mailto:drgeoffh@bigpond.net.au">drgeoffh@bigpond.net.au</a> website <a href="http://www.uoc.otago.ac/departments/msm">www.uoc.otago.ac/departments/msm</a>	Mixture of points, including small group points

## Australian School of Advanced Medicine, Macquarie University - Masters Degree in Musculoskeletal Medicine

Date	Title/Key Resource Person	Venue	Provider	Contact	CME Points
2013	Master of Advanced Medicine in Musculoskeletal Medicine (2-year part-time Distance Learning with 2 on campus Intensives of 1 week each in each year)	Sydney	Macquarie University, Sydney	A/Prof Rod Ayscough or A/Prof Michael Creswick via Scholar Administrator Julie Stone Ph +61 2 9812 3512 Fax +61 2 9812 3600 Email: <a href="mailto:julie.stone@mq.edu.au">julie.stone@mq.edu.au</a> or visit website <a href="http://www.medicine.mq.edu.au">www.medicine.mq.edu.au</a>	

## Australian College of Physical Medicine Fellowship Program

Date	Title/Key Resource Person	Venue	Provider	Contact	CME Points
2013	Fellowship Australian College of Physical Medicine, Part II (Part 1 is Masters in Physical Med or Musculoskeletal Med from Sydney or Macquarie Unis)	Sydney	Australian College of Physical Medicine	Michael Creswick Ph +61 2 9481 9585 <a href="mailto:michael.creswick@mq.edu.au">michael.creswick@mq.edu.au</a> or visit website <a href="http://www.physicalmedicineaustralia.com.au">www.physicalmedicineaustralia.com.au</a>	TBA

## Other Musculoskeletal Medicine Educational Activities

Date	Title/Key Resource Person	Venue	Provider	Contact	CME Points
10-13 October 2013	Burning issues in musculoskeletal medicine <i>What works on the front line</i>	Fairmont Resort Blue Mountains	Australian Association of Musculoskeletal Medicine and Australasian Faculty of Musculoskeletal Medicine	Conference Secretariat: Health Workforce Queensland Telephone: Phone: 07 3105 7800; Email: <a href="mailto:rdobbin@healthworkforce.com.au">rdobbin@healthworkforce.com.au</a>	