



**CHANGED VIBRATION THRESHOLD AND LOSS OF NERVE  
MOVEMENT IN PATIENTS WITH REPETITIVE STRAIN INJURY;  
THE PERIPHERAL NEUROPATHOLOGY OF RSI**

**by**

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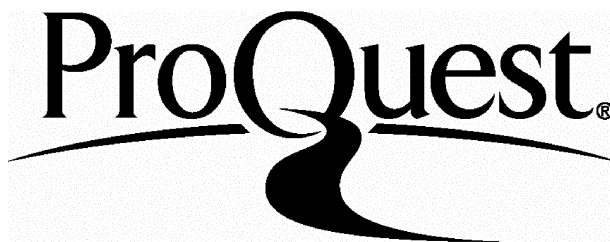
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## **ABSTRACT**

### **Changed vibration threshold and loss of nerve movement in patients with repetitive strain injury; the peripheral neuropathology of RSI**

Repetitive strain injury (RSI) is a chronic pain condition affecting the upper limbs.

It has been associated with tasks that require repetitive and intensive hand activities, particularly when these are carried out in constrained postures.

Patients present with significant symptoms, but when examined, lack signs of specific inflammatory conditions or single peripheral nerve disorder. In consequence there have been considerable problems in the diagnosis of RSI and in designing effective treatment.

Partial injury to peripheral nerves can produce significant symptoms and allodynic changes in the presence of normal nerve conduction studies.

It therefore seemed possible that minor neuropathy might be an important contributor to RSI. To test this, vibration threshold was measured in patients with RSI and in a group of "at risk" office workers. Significantly raised thresholds were found, particularly affecting the median nerve, in both the patients and office workers.

Following five minutes of keyboard use the patients showed a further rise in vibration threshold. Patients also showed reduced tolerance to non noxious suprathreshold vibration. These sensory changes are consistent with the changes observed in patients with diagnosed neuropathy.

In further studies we imaged the median nerve at the carpal tunnel using MRI and high frequency ultrasound. The dynamics of the median nerve were studied during 30 degrees of wrist flexion and extension. A significant quantitative reduction of nerve

movement was seen in patients. A correlation was found between nerve movement measured objectively and a clinical test of median nerve dynamics.

How loss of normal nerve dynamics could contribute to the symptoms experienced by these patients is discussed. It is concluded that minor nerve injury forms part of the pathology of RSI and that testing vibration threshold and examining nerve movement could contribute to diagnosis and prove useful in evaluating treatment outcomes.

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Finally, because I know he would have enjoyed reading this, I would like to dedicate this thesis to my father, William Collie.

## Chapter 1: Introduction

### 1.1 Definition and controversy

Repetitive strain injury (RSI), also called non-specific arm pain (NSAP), is a chronic pain condition of the upper limb. Patients complain of diffuse regional arm pain and tenderness with loss of function that is associated with a lack of objective physical signs. The condition does not conform to traditional medical models of musculoskeletal disease or injury, for example, specific soft tissue inflammation such as tenosynovitis, or of specific nerve entrapment such as carpal tunnel syndrome. As such RSI has become a highly controversial subject among medical practitioners (e.g. Hutson 1994; Mann 1994; Hocking 1992; Semple 1991). Even more controversially the condition appears to be associated with particular work practices and conditions. Occupational examples are office workers who spend long hours using display screen equipment, musicians and production line workers. All have tasks that involve highly repetitive use of the hands combined with constrained and static postures, which have been identified as risk factors for the condition (Serina et al. 1999; Latko 1999), although this is again contested (Hadler 1997). A detailed review of the now strong association between physical work-place factors and the incidence of musculoskeletal disorders has recently been published by the European Agency for Safety and Health at Work, (Buckle & Devereux 1999). Note though that this review covers specific conditions such as carpal tunnel and tendonitis as well as RSI.

Some authors regard RSI as a socio-political phenomenon with elements of mass hysteria (Miller 1988, Lucire 1988, Ferguson 1987). Brooks (1993), set out the British Orthopaedic Associations view of the condition when he stated that the condition had

no “discernible pathological basis”. Others regard it as just normal aches and pains associated with everyday life (Hadler 1990, Brooks 1993). Needless to say this has provoked fierce debate between members of the medical professions (see above), patients and the legal profession.

Since coming into widespread use in the early 1980’s (see Arksey 1998, Chapt. 7) the term "repetitive strain injury" has itself been contentious since aetiology and pathology are implied. A large number of alternative terms have been used to describe this same chronic pain condition (see Table 1.1). Confusingly, RSI is frequently used as an umbrella term for many specific work related musculoskeletal conditions, such as tenosynovitis and carpal tunnel syndrome (Yassi 1997, Yassi 2000). These specific disease entities, where clear diagnostic criteria are available, are not the subject of this thesis. Throughout this thesis the chronic, non-specific upper limb pain condition will be referred to as repetitive strain injury (RSI) or Non-specific arm pain (NSAP).

Table 1.1. Common terms used for repetitive strain injury

Common terms for Repetitive Strain Injury	Acronym	Region(s) where used
Work related upper limb disorder	WRULD	Europe
Occupational overuse syndrome	OOS	New Zealand, Australia
Occupational cervicobrachial disorder	OCB	Japan
Repetitive strain injury	RSI	UK, Australia
Non specific arm pain	NSAP	UK
Cumulative trauma disorder	CTD	United States

## **1.2 Historical background to RSI**

### **Australia**

The term RSI came into widespread use during an apparent epidemic of the condition in Australia during the early 1980's (Feurguson 1987). This coincided with the widespread replacement of typewriters with computer keyboards (Hagberg 1996). Trade union involvement, excessive media attention which profiled RSI as a new occupational epidemic and liberal workers compensation systems have been blamed for the numbers of employees diagnosed (Ireland 1992). Incidence of the condition within employees engaged in the same tasks varied dramatically. Hocking (1987), described an overall 14 % prevalence rate among telegraphists, with 25% of telegraphists reporting arm pain in Sydney and only 4% in Melbourne. Intense debate ensued in the medical literature (e.g. Mann 1994, Brooks 1987, Awerbuch 1987, McDermott 1986). Bell (1989), claimed that RSI was a simulated injury brought about by a reaction to the introduction of new technology, visual display equipment. An inverse relationship between keyboard stroke rate and the incidence of RSI was reported within workers for the Australian Telecom Industry (Hocking 1987). Miller and Topliss (1988), examined 299 patients diagnosed as having RSI. 87% of these patients did not fit any specific rheumatological diagnosis. Although paraesthesia was reported in the painful upper limb by 91% of patients the authors concluded that there was no evidence of physical injury in the majority of their patients.

The Australian National Occupational Health and Safety Commission (1986), defined RSI as "a collective term for a range of conditions characterised by discomfort or persistent pain in muscles, tendons and other soft tissues, with or without physical manifestations. RSI is usually caused or aggravated by work, and is thought to be associated with repetitive movement, sustained or constrained postures and / or forceful movements". This appeared to give RSI a degree of

medical sanction, however the publication of papers in Australian medical journals, which was viewed as a contributory factor in sustaining the epidemic, was much reduced by the mid 1980's (Arksey 1998 Chapt. 2). At the same time statistics regarding RSI were no longer published by the Australian Public Service. In 1985 the Annual General Meeting of the Australian Hand Surgery Society passed a resolution describing RSI as an occupational neurosis, not associated with localised pathology, reversible with normal use and leaving no residual or permanent disability (American Academy of Neurology 1993). A legal judgement in 1987 Cooper versus The Commonwealth, in which an employee lost her claim for damages against the Australian Civil Service, together with the medical response to RSI, appeared to reduce claims for compensation. However as pointed out by Mann (1994), the incidence may have fallen due to better working conditions and worker education on the avoidance of arm pain.

### **The United States**

Cumulative trauma disorder is the term used by the United States Government to describe any musculoskeletal disorder believed to have been caused by activities carried out in the work place. The term therefore covers any musculoskeletal disorder and may include specific conditions such as carpal tunnel syndrome, tenosynovitis and epicondylitis as well as repetitive strain injury. The American Society for Surgery of the Hand expressed their concern that patients with NSAP were being given specific diagnoses, "when the patient has nothing more than the ordinary aches and pains of life" (Weiland 1996). According to Melhorn (1998), 15 – 20 % of all Americans suffer from occupational diseases and he estimated that by the year 2000, 56% of all occupational injuries would be due to cumulative trauma disorders.



## **The United Kingdom**

Cases of chronic upper limb pain associated with repetitive work activity appeared in this country in the early 1980's. The Lancet's September 26<sup>th</sup> 1987 editorial on Repetitive Strain Injury referred to the Australian experience with the condition and argued for increased research towards understanding the pathological processes involved. It was suggested that non-invasive imaging procedures such as Magnetic Resonance Imaging (MRI) should be used to help clarify RSI's natural history. James and Parry (1994), reported that of one hundred musicians examined with upper limb pain, 50% had specific orthopaedic or rheumatological conditions while the remainder had a non specific pain condition of the upper limb which they refer to as RSI. Grundy (1994), argued for a recognition that repetitive actions may indeed cause injury to soft tissue and referred specifically to overuse injuries seen in athletes. Hutson (1994), emphasised that a patient examination that was more comprehensive than the traditional orthopaedic model would lead to a greater understanding of the condition.

Is RSI a new industrial epidemic? Recent reports in the press would lead one to suspect that RSI is a new occupational epidemic, but this is not so. Ramazzini (1713, as reported in Arksey 1998) described the health problems associated with scribes and clerks as: "the maladies that afflict clerks, constantly sitting with incessant movement of the hand". Solly (1886), described "arm pains, numbness and tingling in scriveners". Both reports appear to identify symptoms identical to those described by present day RSI patients.

### **1.3 The social and economic costs**

People with the condition complain that their hand function becomes extremely limited and many have difficulties both with work and every day activities. In this way

RSI has a significant effect not only on individual sufferers and their families, but also on employers due to prolonged sickness, payment for treatment, cost of ergonomic interventions and where workplace conditions have been shown to cause the condition, compensation settlements. Figures for economic cost or even prevalence are difficult to find, partly because of the different terminology used by different countries. However Jayaraaman (1994) reported that in the UK RSI was responsible for a loss of £400 million in lost working days/ year. A recent report by the European Commission (February 2000) stated that work related musculoskeletal disorders of the upper limb and neck cost the European Union up to 2% of its annual gross nation product.

#### **1.4 Diagnosis of RSI**

The UK recently identified surveillance case definitions for work related upper limb pain syndromes (Harrington 1998) and specific subjective criteria for RSI (termed in this report “non specific forearm pain”) were identified. The report sets out diagnostic criteria for a number of specific upper limb disorders including carpal tunnel syndrome, wrist tenosynovitis, epicondylitis and shoulder capsulitis. A “diagnosis of exclusion” of non-specific diffuse forearm pain is proposed for cases where there are complaints of diffuse arm pain, muscle weakness without atrophy, muscle tenderness and allodynia without specific signs of tissue inflammation. The use of these criteria should allow a more accurate estimation of the problem and comparability between research studies.

#### **1.5 Key signs and symptoms of RSI**

The symptoms of diffuse RSI have been described many times e.g. Cohen (1992). Elvey et al. (1986). The patient complains of diffuse wrist and forearm pain, sometimes accompanied by non-dermatomal or single peripheral nerve

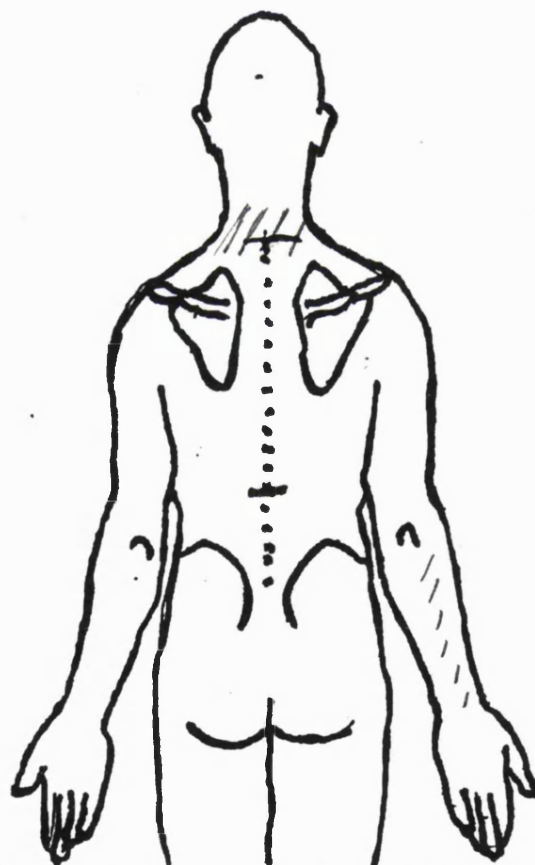
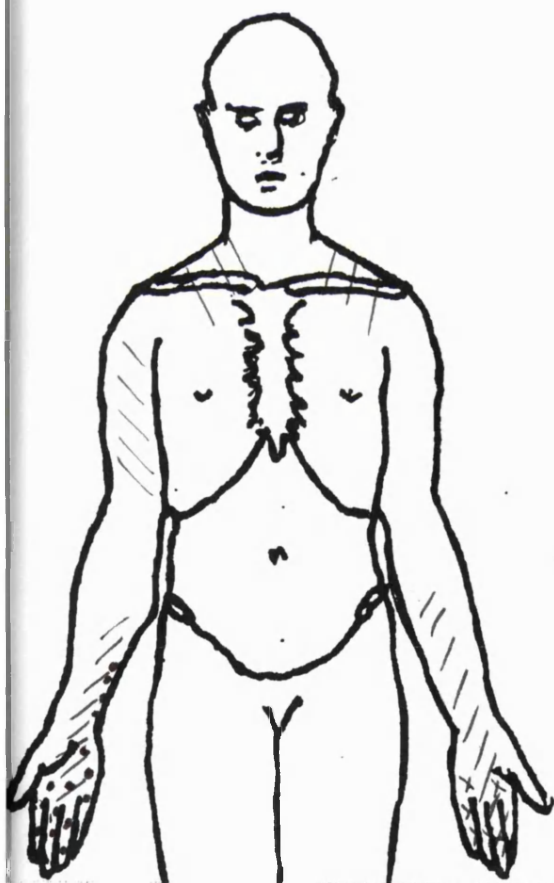
paraesthesia. Symptoms may be unilateral or bilateral and usually are more severe on the dominant side. When severe, symptoms may spread to the upper arm and shoulder girdle and are associated with muscle tenderness, loss of grip strength and mechanical allodynia (Harrington 1998). Signs of tissue injury or inflammation are not apparent. Neck and upper back stiffness may be present but are not associated with radiculopathy. (See Fig 1.1: A typical RSI patient body chart showing areas of symptoms and sensory changes).

Standard neurological examination is normal and where nerve conduction velocities are measured these are within normal limits. Patients do not demonstrate signs of classical peripheral nerve entrapment, for instance they do not exhibit the specific pain referral of carpal tunnel syndrome (CTS) or have nerve conduction abnormalities. Unlike mild carpal tunnel syndrome these patients do not respond to wrist splints or steroid injection to the carpal tunnel. Approximately one third of patients describe marked temperature and colour changes in their hands while a minority have clear signs of autonomic dysfunction (Cohen 1992).

Clinicians who examine these patients using tests of upper limb peripheral nerve mobility (Butler 1991), invariably report positive tests i.e. restricted movement and reproduction of symptoms (Byng 1997). Palpation of peripheral nerve trunks may also be painful and produce paraesthesia in some patients (Hall and Elvey 1999). However nerve palpation and tests of upper limb nerve mobility are not clinical tests used by the majority of the medical profession being almost exclusively used by members of the physiotherapy profession. Butler (1991), a physiotherapist, first described the upper limb tension test 1 (ULTT1), a passive movement test of the upper limb designed to examine dynamics of the median nerve. These tests and their rationale will be described in a later section.

Fig.1.1 Typical RSI patient's body chart showing areas of symptoms and sensory changes

KEY:	////	ACHING PAIN
	•••	PARAESTHESIA
	x x x	NUMBNESS



## **1.6 Possible Causes of RSI**

### **1.6.1 Psychogenic**

What is the evidence that RSI is psychogenic in nature or is entirely caused by psychosocial stresses? A major theme from the medical literature, e.g. Ireland, (1992), Hocking,(1992), Miller and Topliss (1988), is that RSI is either entirely psychogenic in nature or that patients have particular personality disorders such as depression or hypochondria, placing them more at risk of developing a chronic pain condition. Spence (1998), suggests that in the absence of longitudinal studies the association between psychological factors (such as depression and anxiety) and arm pain cannot be seen as cause and effect, since it could equally be effect and cause. The psychological status of RSI patients appears much like other chronic pain patients. Spence (1990), demonstrated that patients with arm pain following accidental trauma have much the same psychological scores for depression and anxiety as those with RSI type arm pain. Weigert et al (1999), examined patients with arm pain and slowing of median nerve conduction velocity at the wrist and those with arm pain without discernable abnormality of nerve conduction studies. No significant difference was found between either group when work satisfaction, depression and health perception were measured. Helliwell (1992) looked for a correlation between levels of depression, anxiety and arm pain in workers engaged in light production work. The only strong correlation found was between arm pain and high risk work practices such as force and repetition.

A recent US Report by the National Research Council (1999) reported that psychosocial factors were more weakly predictive of the incidence of work-related musculoskeletal disorders than were physical work-place factors (such as force or frequency of performing tasks). However this review covered all work-related musculoskeletal disorders, not just RSI.

Whether RSI patients show a greater tendency for illness behaviour in general was addressed by Helme et al, (1992) who found only low scores on a “hypochondria index” in their patients. Finally, a study of who in the workplace hierarchy gets RSI was produced by Bernard,et al. (1994) who looked at the workforce of a large newspaper in the USA. They found just as many editorial as non-editorial staff with problems when the amount of time doing keyboard related tasks was allowed for. Over-riding factors were time spent at a display screen, plus how much of this time was spent working to close deadlines. There were relations between incidence of problems and job satisfaction and boredom, but only within the non-editorial (mainly clerical) group. Even with these workers, the main factor was the amount of time spent working at a visual display screen.

### **1.6.2 Relation of RSI to Fibromyalgia**

The lack of obvious clinical signs has led some authors into diagnosing diffuse RSI as a feature of fibromyalgia (Reilly 1993). Fibromyalgia is a condition of widespread musculoskeletal pain associated with specific muscle and bone tender points, fatigue and emotional distress (Wolfe 1996; Littlejohn 1998). Identifying fibromyalgia sufferers from the normal population depends on the location and number of tender points with little else. However Littlejohn (1998), argues further that fibromyalgia syndrome is an aberrant behavioural response to the complaint of pain in the absence of any initiating tissue damage. Wigley (1998) proposes that many RSI patients later develop fibromyalgia. However the authors’ experience has been that many RSI patients present with a stable condition clearly limited to the upper limb(s). Even over a period of years, the problem does not usually spread to involve other body regions. The inclusion of RSI into the fibromyalgia category, itself a contentious condition (Quintner and Cohen 1999; Cohen and Quintner 1998), is interesting. Cohen and Quintner (1998) refer to fibromyalgia as the “new psychogenic”

rheumatism. In any compensation system based on objective impairment, the absence of any demonstrable evidence for pain may deny the sufferer access to compensation. This criterion, combined with the lack of association with work activities (although see Wigley 1999), makes it tempting to reclassify RSI as regional fibromyalgia, thereby giving it a more “respectable profile”. However tempting this is, a diagnosis of fibromyalgia (a functional state of lowered pain threshold) does not address problems of causation or pathology. Overall, the question of the relationship between RSI and fibromyalgia must still be considered uncertain.

### **1.6.3 Direct nociceptive causes of RSI**

Possible chronic activation of muscle nociceptors could occur either through tissue pathology (Dennet and Fry 1988) or ischaemia (Pritchard et al. 1999).

Dennet and Fry (1988) examined muscle biopsy samples from the first dorsal interosseous muscle in 29 women complaining of non specific arm pain. They observed increased type1 fibres, decreased type 2 and also changes to mitochondria (red ragged edges). They conclude that muscle overuse was the cause of symptoms. However such changes may be a consequence of muscle adaptation to prolonged use and not necessarily a cause of symptoms (Jones and Round 1992). Pritchard et al (1999), observed the relative constriction of the radial artery and its failure to dilate with exercise in a group of patients with RSI. They conclude that physiological claudication due to inhibition of local nitric oxide function was responsible for diffuse forearm pain. In these subjects artery diameter responded normally to inhaled glyceryl trinitrate leading to the conclusion that nitric oxide dysfunction was a result of pain inhibition. Cause and effect are not therefore clear and these observations do not explain why pain symptoms continue when patients rest the affected limb or account for the allodynic responses that are commonly reported. However a lack

blood flow response to exercise may reflect a change in neurogenic control and is not inconsistent with neural pathology.

Independent evidence for local activation of nociceptors in joint and muscle is lacking. Low force muscle activity sustained for long periods involves the continuous recruitment of low threshold motor units. Such activity may possibly lead to necrotic changes in the muscles affected (Sjogaard and Sogaard 1998). However studies to gauge musculoskeletal stress during repetitive work activity by studying biochemical markers related to muscle damage such as creatine kinase (CK) have been few and the results equivocal (Hagberg et al. 1982, Mathiassen et al. 1993). *enzyme energy metab.*

Symptoms of myofascial origin have been proposed as a component of the clinical picture seen in RSI. Myofascial pain is based largely on the presence of "trigger points" within muscle which produce a characteristic aching (Simons and Travell 1984). Quintner and Cohen (1994) dispute that pain produced by trigger points is due to muscle C fibre afferent input and argue that symptoms are due to "secondary hyperalgesia of peripheral nerve origin". Certainly, a comparison between the course of cutaneous peripheral nerves in the cervical spine, shoulder girdle and arm (Williams et al. 1989) show a similar distribution to maps of trigger points and their pain referral patterns. There may be a degree of convergence here with the possibility of peripheral nerve origin for the pain in RSI, as discussed in more detail below. On the general question of how far nociceptive input from musculoskeletal tissues is directly responsible for RSI, none of the evidence is compelling, although a role for such inputs certainly cannot be ruled out.

#### **1.6.4 Neuropathic causes**

There are clearly some similarities between RSI and entrapment neuropathies. For example carpal tunnel syndrome, a common nerve entrapment that affects the



median nerve at the wrist, presents with pain and paraesthesia in the median nerve distribution of the hand and wrist and difficulties with gripping activities. However as discussed earlier there are features of RSI that do not match those of single entrapment neuropathies. As described previously, palpation over nerve trunks and tests of nerve dynamics often produce pain and paraesthesia in RSI patients. RSI patients have also been reported to show a reduced flare response following the application of capsaicin (Helme 1992), a change that is consistent with small sensory fibre loss. Multiple levels of minor nerve injury, in which fascicular loss is not sufficient to show up on electro-neurophysiological tests (Brumback et al. 1992, Spindler et al. 1990), is a possibility.

## **1.7 My Interest in RSI**

As a clinical physiotherapist treating patients with RSI, I became intrigued by the homogeneity of their symptom presentation. Even in the absence of abnormal nerve conduction studies patient's described their symptoms as follows:- allodynia to light touch, burning pain made worse with movement and frequent complaint of paraesthesia. These symptoms I felt indicated some neuropathic involvement. This thesis forms my search to find explanations for this chronic and disabling arm pain.

## **Chapter 2:       Minor Nerve Injury**

What is the evidence that painful symptoms may follow minor nerve injury when signs of changed nerve function are not apparent? Before attempting to answer this question a review of the anatomy of the peripheral nerve will be helpful.

### **2.1    Anatomy of a peripheral nerve trunk**

The nerve trunk is a composite tissue with the sole function of protecting the nerve fibres and maintaining their blood supply. Nerve fibres are packed within endoneurial connective tissue and organised into fascicles by the perineurium. The perineurium is a connective tissue and cellular barrier of considerable tensile strength that acts to limit diffusion, thus protecting the interior of the fascicles by maintaining their chemical environment. The epineurium is the outer connective tissue that supports and protects the fascicles and carries the extensive vascular system that sends branches through the perineurium to form the endoneurial vessel system. (See Fig. 2.1 Anatomy of a peripheral nerve trunk and Table 2.1 Classification of sensory nerve fibres). Vessels pass through the perineurium obliquely into the endoneurial space. At these points the vessels are particularly vulnerable to compression if there is an increase in pressure, for example, caused by an increase in intrafascicular fluid pressure due to oedema. A major component in maintenance of the chemical environment of the nerve fibres is the blood-nerve barrier of the endoneurial capillaries. The closely apposed endothelial cells of these capillaries form a barrier to macromolecules and other substances in the circulating blood. The perineurial diffusion barrier together with the blood nerve

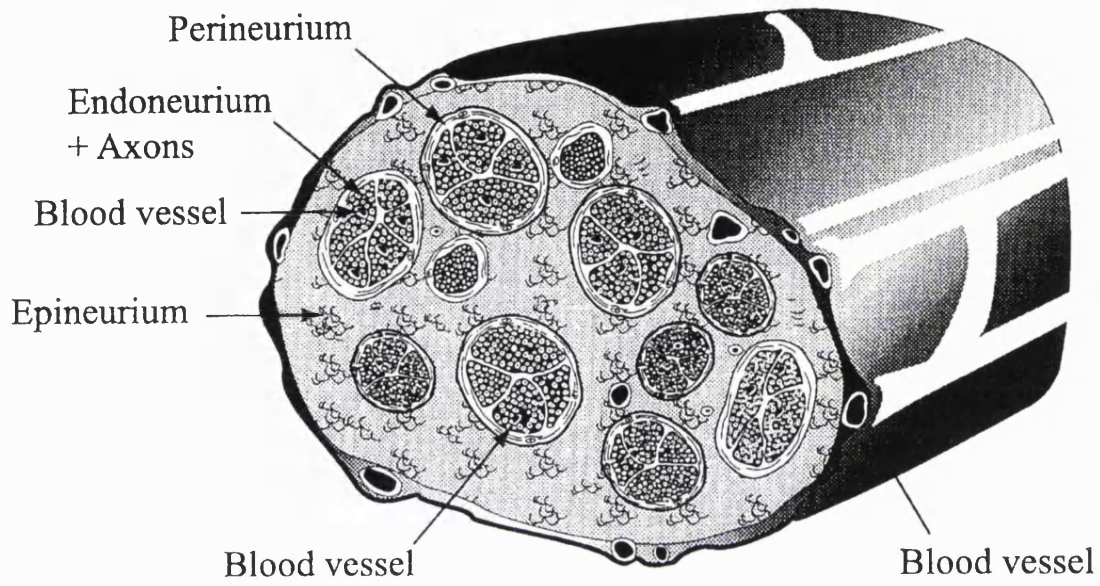


Fig 2.1 Anatomy of a peripheral nerve trunk

Table 2 1. Classification of sensory nerve fibres

<b>Classification</b>	<b>Morphological fibre type</b>	<b>respond to:</b>
A $\beta$	Large myelinated fibres	Different types of mechanoreceptor responding to innocuous stimuli Examples: <ul style="list-style-type: none"> <li>• Pacinian corpuscle-vibration;</li> <li>• Meissner`s corpuscle-light touch.</li> </ul>
A $\delta$	Small myelinated fibres	<ul style="list-style-type: none"> <li>• Mechanoreceptors</li> <li>• Cold-sensitive thermoreceptors</li> <li>• Nociceptors responding to noxious pressure and heat</li> </ul>
C	Non myelinated fibres	<ul style="list-style-type: none"> <li>• Warm sensitive thermoreceptors</li> <li>• Nociceptor responding to noxious pressure, heat and irritant chemicals</li> </ul>

barrier are essential for the maintenance of the endoneurial environment. A loose “adventitia “ surrounds the nerve trunk allowing it to slide in its nerve bed (Lundborg 1988).

### **2.1.1 Nerve sheath innervation**

Nerve sheaths are themselves innervated via local axonal branching and by the closely associated vasa nervorum of the perivascular plexus (Hiromada 1963). These unmyelinated or finely myelinated nerves (Thomas 1963), the nervi nervorum, have recently been shown to contain both substance P and calcitonin gene related peptide (Zochodne and Ho 1992, Zochodne and Ho 1993, Sauer et al 1992).

Electrophysiological data (Bove and Light 1995) has demonstrated both their nociceptive function and their receptive fields in muscle and tendon. Bove (1997) and Zochodne (1992), postulate a “nocifensor” function for the nervi nervorum in the resulting hyperaemia that follows nerve damage or capsaicin application to the nerve sheath.

## **2.2 Minor Nerve Injury Models**

Recently animal models have been developed that allow the study of minor nerve injuries. These have shed light on the mechanisms underlying the neuropathic symptoms seen with these injuries.

Animal models of painful peripheral neuropathy include tight partial nerve ligation (Seltzer 1990), ligation with partial nerve transection (Chung 1993), peripheral neuritis (Maves 1993, Zochodne 1993, Eliave 1996) and chronic constriction injury (CCI) (Bennett et al 1988, Munger et al 1992). In animals, body posture, measurements of paw withdrawal latency in response to heat, mechanical stimulation and sympathetic

manipulation are used as indicators of spontaneous pain, allodynia and hyperalgesia (see Table 2.2). The animals affected limb posture (guarding posture) is assessed as a indicator of spontaneous pain behaviour.

Table 2.2 Abnormal sensations associated with neuropathic pain

Hypoesthesia	Diminished sensitivity to stimulation
Hyperalgesia	An increased response to a stimulus which is normally painful
Allodynia	Pain due to a stimulus that does not normally provoke pain e.g. light brushing of the skin

Tight partial nerve ligation and ligation with partial nerve transection will not be considered further, as in both of these models neural damage is such that severe sensory loss and motor weakness are clearly apparent. However the chronic constrictive and neuritis model will be considered in some detail as these injuries may represent neuropathies which may underlie the neuropathic pain syndromes that occur without significant clinical signs of nerve damage.

### 2.2.1 Chronic constrictive injury

This experimental model, first performed by Bennett et al (1988), consists of four loose chronic gut ligatures that are tightened around a rat sciatic nerve until the nerve is observed to be just indented and neural blood flow is shown to be retarded but not arrested. The sciatic nerve in this region of the thigh is loosely connected to surrounding musculature by thin connective tissue. A sham operation in which the nerve is gently freed from this tissue and the wound sutured is performed on the contralateral leg or

performed in a control group. Pain related behaviors are seen to occur by day 1 following the experimental procedure and reach maximal intensity by the end of the first to second post operative week (Guilbaud 1993, Atall et al.1994). The animals specifically demonstrate hyperalgesia and allodynia to thermal stimuli, with a variable response intra and interstudy to mechanical stimulation. Such variability in response to mechanical stimulation may reflect different protocols for mechanical testing. Over 14 -28 days the ligatures are progressively absorbed and abnormal pain related behaviours gradually disappear.

Morphological changes that appear to parallel the time course of pain behaviours have been studied within the nerve and the spinal cord. The nerve appears grossly swollen either side of the proximal and distal ligatures with marked narrowing at the site of constriction, most prominent by week 3. In effect, stasis of venous return causes increased endoneurial fluid pressure which results in a self strangulation injury to the nerve (Myers et al.1993). This closely resembles the ischaemic model of neuropathy first described by Sunderland (1976).

Fibrosis surrounding the nerve and its adherence to surrounding musculature is also reported over the first few weeks and although this decreases, it is still present at week 15. Fibrosis surrounding the nerve, but to a lesser extent, is also apparent following sham operation (Sommer 1993). Mosconi and Kruger (1996), observed connective tissue proliferation following the application of polyethylene cuffs to the sciatic nerve causing the nerve to become adherent to adjacent muscle. This tissue proliferation was also observed when pieces of chromic gut were laid alongside the nerve. Fibrosis is a normal response to inflammation and would have significant consequences for neural dynamics. In reviewing the resulting morphological changes and their time course it is

important to remember that this injury is acute in onset with resolution over a few months, and therefore may not fully represent the more gradual and chronic peripheral nerve irritation and compression that occurs in patients.

After CCI, a consistent and highly significant loss of A $\beta$  fibres is observed by most authors, peaking at 2 weeks post surgery when pain related behaviours have started to diminish. At week two following nerve injury most nerves fibres are regenerating (Coggeshall 1993). However when most pain related behaviors have disappeared, week 8-10, A $\beta$  fibre appearance is still abnormal with respect to their diameter and overall number (Guilbaud 1993). The extent to which large fibre loss is responsible for pain symptoms is therefore not clear. Damage to C and A $\delta$  fibres occurs over the same time period but to a lesser extent than the myelinated fibres (Basbaum 1991, Coggeshall 1993). Guilbaud (1993) observed that the time course of abnormal pain related behaviors in the rats followed both the A $\delta$  degenerative and regenerative phase. At the time that most of the abnormal pain behavior had recovered, week 3, A $\delta$  nerve fibres had returned to their original number and size. It is important to note that axonal damage was not observed to be consistent across all fascicles, some fascicles being relatively spared and other showing extensive axonal loss.

Along with the morphological changes, afferent fibres develop changed firing patterns following CCI. Spontaneous A $\beta$  fibre firing occurs that is correlated with the presence of mechanical hyperalgesia (Tal and Eliav 1996). Changes in C fibre function have been observed following the CCI injury (Koltzenburg 1994a) and given that most C fibres are nociceptors, may be more relevant to pain. More than 10% of C fibres showed spontaneous activity during the first week following the experimental procedure,



returning to normal levels (~2%) over the following 3 weeks and showing a further peak of activity two to four months post injury. Nociceptive C fibres had increased mechanical threshold and were thus unlikely to be responsible for the mechanical hyperalgesia observed in this model. However the reverse was true for heat stimuli, with the C fibres in CCI nerves demonstrating increased activity to heat stimuli, a change that may be important in the development of heat hyperalgesia, a consistent behaviour with this model. Many C fibres, including some with low levels of spontaneous activity, were observed to increase their activity to noradrenaline application. C fibres acquiring novel sensitivity to sympathetic out flow may help explain sympathetic maintained pain states observed clinically. Changed patterns of afferent firing initiate and maintain changes in the central nervous system that underlie the changes in function and excitability thought to be important in pain production. These changes will be discussed in greater detail in 2.3.3.

### **2.2.2 Neuritis Model**

The extent to which the inflammatory reaction around the nerve in the CCI model contributes to the hyperalgesic response has been investigated in rats. Maves et al.(1993), used both chromic gut, plain gut and silk suture material. Ligatures were applied loosely such that they were free to slide along the nerve. Little or no axonal pathology was observed in this model and heat hyperalgesia was observed in only those rats where chromic gut was used. No mechanical hyperalgesia was observed in any group. Interestingly heat hyperalgesia was observed in this experimental procedure when strips of chromic gut material were laid alongside the sciatic nerve, with no ligation at all. Bennett (1994a), has referred to the Maves model as a neuritis and specifically refers to inflammation of the nerve sheath being a component of nerve damage.

Clatworthy et al (1995) demonstrated that dexamethasone reduced the inflammatory response induced by loose suture ligation and blocked the development of guarding behaviour and thermal hyperalgesia. Eliave et al. (1999) investigated the consequences of inflammation of the sciatic nerve sheath by the application of carrageenan or complete Freund's adjuvant. The control groups received either sham operations or a small area myositis of the biceps femoris muscles induced by Freund's adjuvant. Sensory investigations, carried out over the hind paw, demonstrated mechano, heat and cold allodynia only in the neural inflammatory group. These sensory changes occurred without axonal damage and could therefore occur in the clinical situation in the absence of significant detectable structural nerve damage. Note, however, that not all investigations have seen effects just from nerve inflammation. Thus Sommer (1993) found moderate epineurial fibrosis but no behavioral changes in the sham operated rats where loose sliding ligatures were applied, whereas ligatures applied according to the CCI protocol produced the expected behavioural changes and axonal pathology.

The peripheral nerve sheath has received little attention both in its response to injury and its potential contribution to symptom production. Zochodne (1993) demonstrated an extensive neurogenic vasodilation in the peripheral nerve trunk in response to capsaicin application, while Bove (1995) demonstrated the presence of calcitonin gene related peptide (CGRP) in the nervi nervorum of epineurial nerve sheaths. Both Substance P and CGRP are neuropeptides involved in nociception and the presence of sensory C fibres in the nerve trunk (nervi nervorum), suggest that they will respond to stimuli occurring during nerve damage such as mechanical pressure and tension as well as inflammatory processes. Their position suggests that they are particularly vulnerable in chronic compression and friction syndromes. A consistent feature of RSI and many other

neuropathic conditions is nerve trunk pain on palpation. This plus the restriction of limb movement when testing neural mobility, could be a result of sensitisation of nociceptor afferents in the nervi nervorum. However electrophysiological recording from the nervi nervorum presents considerable technical difficulty, and therefore its contribution to the sensory input to the dorsal horn remains to be evaluated.

## **2.3 Consequences of nerve damage**

Damage to peripheral nerves may cause a range of dysethesias. These are due to both peripheral and central neuronal changes.

### **2.3.1 Peripheral Changes**

In the neuritis model with little or no axonal loss and in the early stages of CCI when inflammatory reaction predominates, the release of cytokines (substances released by cells of the immune system that act locally and systemically) following the invasion and activation of macrophages and fibroblasts would contribute to the sensitisation of nociceptive fibres and therefore hyperalgesia (Sorkin et al.1997). Pro inflammatory cytokines expressed by fibroblasts and macrophages may gain access to axons following changes to the perineurium and vascular endothelial cells (Mizinsin 1990, Lundborg 1988). These changes include interruption of the perineurium and hypertrophy and proliferation of endothelial cells. In addition, one month following CCI injury, aberrant axonal sprouts outside the perineurium were also observed (Sommer et al.1998a, Sommer and Myers 1996, Sommer et al. 1993). Blocking the actions of one cytokine receptor, tumour necrosis factor receptor1, following CCI in rats, significantly attenuated both the intensity and duration of mechanical and heat hyperalgesia (Sommer et al. 1998(b)). Increased nitric oxide (NO) levels have been observed in the

endoneurium of CCI nerves (Levy and Zochodne 1998). NO, previously identified with a role in inflammatory reactions may directly or indirectly, enhance nociception by activating local C fibres (Holthusen and Arndt 1995). Levy et al (2000), has shown an early and transient expression of NO in injured nerve fibres and that the mechanosensitivity of A $\beta$  fibres that follows CCI may be blocked by the local administration of L-NAME.

At the site of trauma where axons are damaged they may form a neuroma. These sites may become areas of spontaneous ectopic impulse generation (Devor 1994, Meyer 1985) where nerve impulses are generated in the absence of a specific stimulus. They also show abnormal sensitivity and generate impulses following minor mechanical, temperature or chemical stimulation. For example, following CCI damaged C fibres become sensitised to noradrenaline. This occurs via an upregulation of  $\alpha$  2 receptors on the neuronal membrane at the site of nerve damage at receptive terminals (Sato and Perl 1991, Perl, 1994, Campbell 1994). Even normal levels of sympathetic outflow may therefore result in increased symptoms. Sympathectomy prior to CCI significantly decreased thermal hyperalgesia but did not alter the mechanical hyperalgesic response (Dermeules 1995). The sympathetic postganglionic neurone contribution may be independent of preganglionic sympathetic outflow from the central nervous system, suggesting a novel mechanism by which sympathetic terminals can regulate sensory activity (Kinnman and Levine 1995). Sympathetic sprouting at the dorsal root ganglion has also been observed experimentally and may be another method of evoking abnormal spontaneous discharge following peripheral nerve damage (Chung et al 1993, McLachlan 1993, Wall 1974, Thompson 1997). In contrast Kim et al (1999) studied sprouting of the sympathetic nerves at the dorsal root ganglion following transection of

the S1 and S2 caudal nerves in two groups of rats. Only one group showed significant signs of allodynia. Histological staining of the injured dorsal root ganglia revealed the degree of penetration of sympathetic fibres to be the same in both groups. However quite minor manipulation of a peripheral nerve can sometimes trigger the development of sensitivity to noradrenalin or sympathetic stimulation. For example the application of a stretch to an exposed nerve changed the terminals of nociceptive C fibres such that they now demonstrated firing to noradrenaline stimulation (Sato and Perl 1991).

To sum up, peripheral changes caused by partial nerve injury are extensive. C fibres at their termination sites, and at the site(s) of trauma along the nerve trunk, demonstrate lowered threshold for stimulation, increased frequency of firing and spontaneous activity. A novel sensitivity to noradrenaline stimulation may develop and evidence suggests that normal levels of sympathetic activity may provoke C fibre firing. The abnormal activity of C fibres produces aberrant input to the dorsal horn over long periods following minor nerve trauma (see Fig 2.2).

### **2.3.2 Role of Neurotrophins**

Neurotrophins, for example nerve growth factor (NGF), are large peptides produced by a number of cell types including muscle cells, basal keratinocytes in the skin and by Schwann cells in peripheral nerves. They are essential for the survival of the immature nervous system, and play a role in regulating function in the adult nervous system.

Neurotrophins derived from target tissues are transported from nerve terminals to the cell body by retrograde axoplasmic flow. Changes in nerve fibre diameter and loss of axons and of receptors for neurotrophins follow nerve injury (e.g. Dahlin et al. 1986; Tanoue et al. 1996) reducing the amount of neurotrophin available to the nerve cell

body. Peripheral and central neurons involved in pain signaling appear critically dependent on the amount of NGF to which they are exposed. Elevated levels of NGF following inflammation appears to sensitise C fibres either directly or indirectly via immunocompetent cells (Woolf 1995, Andreev 1995, Koltzenburg et al 1999). Decreased levels of NGF available to the sensory cell bodies following nerve injury have several effects on sensory neurones which include changes to peptide expression. Changes are complex with some peptides falling in concentration (eg Sub P, Calcitonin gene related peptide) others rising (eg Galanin) (McMahon et al. 1997, Xu J et al. 1996). A de novo expression of Sub P occurring in A $\beta$  fibres following axotomy has been demonstrated and may be a means whereby low threshold A $\beta$  fibre input could lead to Sub P mediated touch allodynia (Malcangio 2000). Peptide changes will alter synaptic function in the dorsal horn and may be involved in increasing the receptive field of central neurons as discussed in the next section. Nociceptors sensitive to NGF also express brain derived neurotrophic factor (BDNF). Levels of BDNF in nociceptive neurones and their terminations in the dorsal horn are regulated by NGF (Michael et al 1997). Like other neurotrophins BDNF is a trophic factor for sensory neurones and also regulates the mechanosensitivity of slowly adapting mechanoreceptors. Following both inflammation and axotomy BDNF is upregulated within the spinal cord. Nerve damage and inflammation also produce an upregulation of BDNF in A $\beta$  neurones (Mannion et al 1999). Elevated levels of BDNF within the spinal cord may cause changed neuronal connection within the dorsal horn. Novel synaptic connection between neurones within the deeper dorsal horn laminae with neurones in the superficial laminae may partially explain mechanical allodynic responses mediated by A $\beta$  input from the periphery

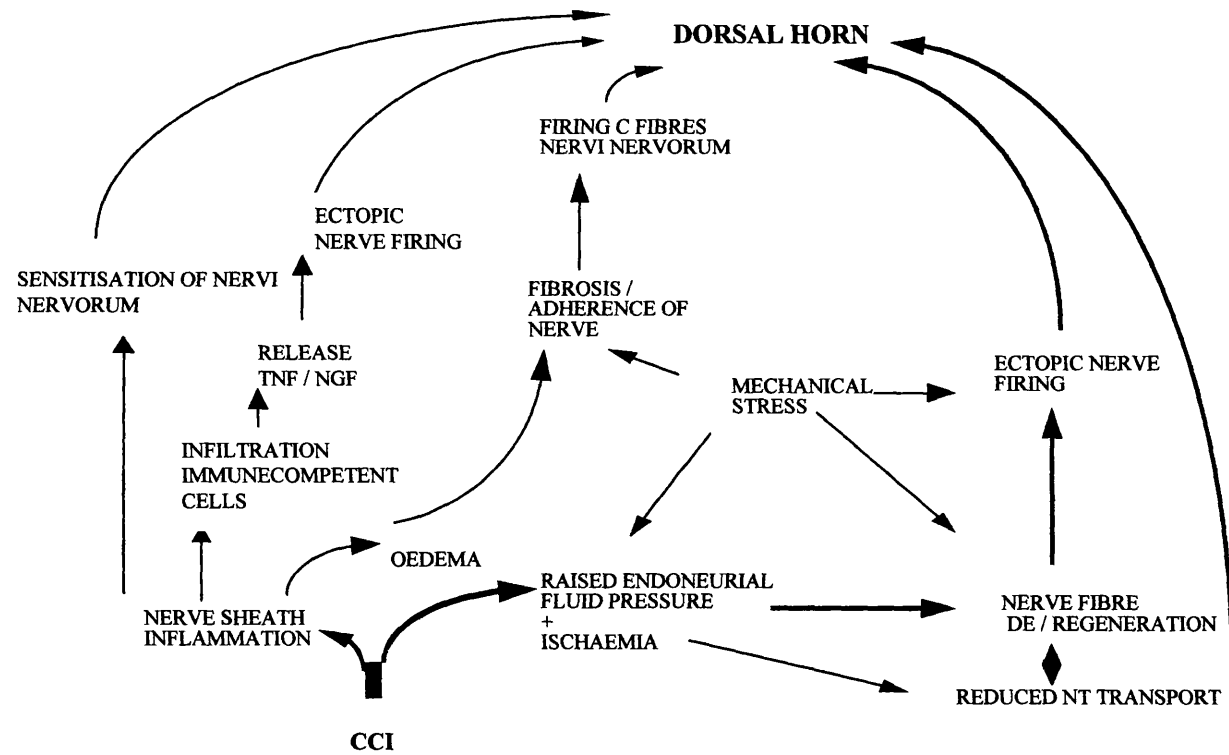


Fig. 2.2 Summary of peripheral changes following nerve injury

Key CCI chronic constriction injury, NT neurotrophin

BDNF also appears to have a significant amplifying effect on spinal cord excitability, as measured by recording ventral root potential to C fibre input (Kerr et al 1999).

Pretreatment of animals with NGF to elevate spinal levels of BDNF increased this C fibre reflex activity (Boucher et al 2000).

Supplying exogenous NGF to damaged peripheral nerves within the first 3 weeks following CCI injury can reduce the resulting hyperalgesia (Ren et al. 1995). However NGF antibodies can also reduce the effects of CCI (Herzberg et al. 1997) so the changes seen in CCI cannot just be a consequence of reduced NGF availability. The CCI model involves both nerve sheath inflammation and wallerian degeneration, both processes that lead to local elevation of NGF levels. While increase in NGF will cause C fibre sensitisation and increase the excitability of dorsal horn neurones (Lewin et al 1993, Donnerer et al. 1992.), decreased retrograde transport of NGF following nerve injury mediates novel spinal synaptic connections as discussed above. Human studies of levels of NGF in peripheral nerves following injury (Anand et al. 1997) demonstrated reduced levels in injured nerves and dorsal root ganglia, but found normal levels of NGF distal to the injury, with areas of high NGF concentrations at neuroma formations. This suggests that early NGF administration may help prevent neuronal degeneration while at later stages anti NGF treatment may help relieve chronic pain.

Glial cell line-derived neurotrophic factor (GDNF), a member of transforming growth factor- $\beta$  (TGF- $\beta$ ) group, has survival promoting effects on mid brain dopaminergic neurones (Beck et 1995) and motor neurones (Yan et al 1995). GDNF also has a supportive role on a sub population of C fibres (IB4 binding neurones) following embryonic development (Molliver et al 1997). Following nerve injury, intrathecal administration of this neurotrophin appears to have a protective effect on this population of C-fibres and prevents the axotomy induced sprouting of A $\beta$ -fibres into the superficial



layers of the dorsal horn (Bennett et al 1998). While, unlike NGF, GDNF appears to have no acute sensitising role on C fibres, evidence suggests it has both neuromodulatory and trophic effects (Boucher2000). Finally nerve injury causes reduced axonal size due to a loss of cytoskeletal structures. Following nerve injury, treatment with NGF and GDNF restores C fibre neuronal size and conduction velocity (Bennett et al 1998).

Apart from changed neurotrophic expression and uptake that occurs following nerve injury, nerve compression itself will have detrimental effects on the transport of neurotrophins. A consistent feature of CCI, with ligature or polyethylene cuff application, is proximal and distal nerve swelling at treatment sites (Bennett 1988, Mosconi 1996). This is observed by day three post operatively and may be due to a blockage of anterograde and retrograde axoplasmic flow as well as the associated neural oedema. Although measurements of pressure applied to the nerve have not been sought in these experimental nerve injuries, reduced axoplasmic flow has been demonstrated with relatively small increases in pressure around a nerve. Dahlin and McLean (1986), found that 20 –30mmHg applied for eight hours to a rabbits sciatic nerve resulted in the inhibition of fast and slow axonal flow. Pressures of this magnitude have been recorded within the carpal tunnel both in carpal tunnel patients and also in asymptomatic subjects when the wrist is held in extended and flexed positions (Gelberman 1981, Keir et al 1998). Low levels of Vinblastine, a transport blocker, significantly reduced both the chemical sensitivity of the C afferents and their ability to produce neurogenic oedema. . This occurred without change to behavioural thermal responsiveness and with no evidence of neuronal degeneration (Fitzgerald et al 1984). It is feasible that alterations in axoplasmic flow will reduce the transport of neurotrophins to the nerve cell body. This may produce change both to neuropeptide expression

centrally and peripherally and may also result in change of neurotrophin levels within the spinal cord. This could occur without significant axonal loss or clinical sign of nerve injury.

### **2.3.3 Central Nervous System Changes**

Abnormal C fibre input and the loss of A $\beta$  fibre input to the dorsal horn leads to changes in CNS sensitivity and in sensory processing (McMahon 1993, Woolf and King 1990, Devor 1988). A key change is C fibre evoked central hyperexcitability or “wind up” involving N-methyl D-aspartate (NMDA) receptor activation (for example see Dickenson 1997, Kim et al. 1997). These central nervous system changes probably underlie secondary hyperalgesia where areas around zones of injury or inflammation show an increased response to a range of stimuli (Sang et al. 1996). Normally, significant divergence and convergence of sensory input occurs within the dorsal horn with adjacent neurons having overlapping fields. In CCI rats, increase in the size of a receptive field occurs and this is likely to result in symptoms that may spread outside of “normal” dermatomal boundaries (Cook et al 1987).

The initial extensive loss of A $\beta$  fibres in the CCI model and therefore loss of peripheral inhibitory modulation at dorsal horn level may be related to the onset of pain behaviour. Studies on rats with soft tissue inflammation and nerve damage demonstrate that these hyperexcitable states lead to the death of some neurones in the I and II laminae in the dorsal horn. This region is known to contain significant numbers of inhibitory interneurons, and continued hyperexcitability may be due at least in part to a general lowering of the surrounding inhibitory field (Woolf and Wall 1982).

Abnormal and novel sensory input with loss of inhibitory mechanisms results in the sensitisation of dorsal horn neurons concerned with the ongoing transmission of

information to higher centres. This changed response means that relatively minor noxious as well as non noxious sensory input results in an amplified pain response. The extent of central sensitisation may depend on the initial level of excitation at the dorsal horn prior to injury. Seltzer (1991) demonstrated increased levels of abnormal pain related behavior in rats after using a electrical conditioning stimulus of C fibre strength prior to nerve injury. This indicates that prior to nerve injury noxious stimuli, such as input from an inflamed nerve sheath, may create a "conditioning effect" on the central nervous system that would amplify the effect of nerve injury. This may make subsequent afferent input from the injured nerve more effective in producing the central neuronal changes that underlie central sensitisation.

Controversy exists as to what extent changes within the CNS become self perpetuating or require ongoing noxious peripheral input to maintain them. In animal experiments central sensitisation does not outlast peripheral noxious stimulation by more than one hour (Niv 1993). Pain of peripheral origin is amplified by central sensitization (Dickenson 1997) and this amplification appears to be maintained while the peripheral source of noxious stimulation exists. Clinically, nerves blocks in the periphery can abolish or significantly reduce long standing areas of hyperalgesia, allodynia and presumed sympathetic reflex abnormalities (Campbell et al. 1988, Thiminue et al 1996). These results suggest that, for the most part, central changes require continuous sensory input to maintain them.

The marked widespread allodynia seen in RSI is consistent with central sensitisation. Cohen and Arroyo (1992) concluded on the basis of symptom presentation and subject responses to electrical stimulation, that RSI is largely a central sensitization phenomenon with secondary hyperalgesia related to abnormal C fibre function. This

may overstate the situation a little, but, as in many other chronic pain states, central sensitisation is likely to play an important role.

## **2.4 Clinical Consequences**

Injuries involving chronic constrictive or nerve sheath inflammation may occur in humans where nerves are subject to compression, mechanical irritation or torsion, and excessive pressure for e.g. spinal bony nerve root entrapment, carpal tunnel syndrome, traction injuries to the brachial plexus.

Microneurographic studies have allowed some of the basic mechanisms involved in pain and other sensory phenomena that accompany neuropathic conditions to be studied in man. Recordings made from nerve fibres while the subject undergoes psychophysical testing has demonstrated peripheral sensitisation of nociceptors in a patient with neuropathic pain (Cline et al. 1989).

A $\beta$  fibre centrally mediated mechanical hyperalgesia in a human experimental model has also been demonstrated (Torebjork 1992) and may be maintained by sustained peripheral nociceptive activity (Anderson 1995). Damaged and ischaemic A $\beta$  fibres acquire abnormal sensitivity and will discharge ectopically (Bostock 1994). Abnormal A $\beta$  fibre activity will produce paraesthesia in humans and in the presence of central changes to the normal processing of sensory A $\beta$  input may also produce painful symptoms (Cervero 1994, Campbell 1988). The severity of mechanical allodynia associated with chronic painful neuropathy was found to closely correlate with the intensity of background pain. In these patients blocking A $\beta$  fibres eliminated touch evoked pain, but spontaneous pain persisted when only C fibres were conducting. (Koltzenburg et al 1994b). Lang et al (1995) found pain intensity in carpal tunnel syndrome (CTS)

correlated with impairment of large myelinated fibres and they suggested that sensitisation of the nervi nervorum due to pressure changes within the carpal tunnel together with central changes in sensory processing could explain the pain symptoms.

As discussed earlier, minor nerve trauma and compression has been shown to have significant consequences for the production of painful symptoms and altered sensory sensitivity in animal models. It is not unreasonable to expect that minor nerve injuries in humans would produce similar effects, (Dellon and Mackinnon 1986). A significant number of patients with conditions such as non-specific arm pain, will present with positive symptoms usually associated with peripheral nerve injury, e.g. paraesthesia, hyperalgesia and allodynia, spontaneous pain and loss of function, but will have normal reflexes, muscle power and sensitivity on qualitative tests. Frequently sensory nerve conduction studies will either show minor changes or also be reported as normal. In the CCI / neuritis model many axons are either undamaged or suffer partial damage. Undamaged fascicles would account for the normal nerve conduction results. In contrast, quantitative tests of somatosensory function, particularly vibration, will be abnormal prior to changes in nerve conduction velocity and can be used to identify subtle changes in nerve function (Jetzer 1991, Dellon 1980). A good clinical example of a neuropathic pain which persists despite an apparent lack of objective neurological signs is post herpetic neuralgia where, following infection of the sensory nerve by the herpes virus, pain and allodynia may continue after resolution of the cutaneous vesicular eruptions (Bennett 1994b). No major signs of continuing nerve damage are present, but quantitative sensory testing showed changed thresholds with marked allodynia (Rowbotham and Fields 1996).

Due to the obvious ethical and practical difficulties in carrying out experiments in humans, neuropathological findings following minor nerve lesions are sparse compared to the extensive data available in the animal CCI and neuritis models. An important paper (Mackinnon et al. 1986) identified similar morphological changes to the CCI/neuritis animal model in biopsy studies of chronic compressive injuries of human sensory radial nerves. All of the patients (n=4) complained of burning pain in the distribution of the sensory radial nerve. In two cases there was minor axonal damage, in a further two cases nerve fibres were not damaged but changes to the connective tissue sheaths were similar to those seen in the neuritis model (Eliave1999, Maves 1993). Symptoms of nerve origin are therefore possible without nerve fibre damage as previously hypothesised by Ashbury and Fields (1984).

## **2.5 Conclusion**

In conclusion, the consequences of minor nerve injury may be more severe and more common than previously suspected. The experimental models described represent a range of injury from minor inflammation of the nerve sheath to more severe neural constriction with significant nerve fibre loss. Both ends of the spectrum result in pain due to neural pathology, the more extensive injury will result in positive findings of sensory loss. Abnormal input from damaged or ischaemic nerve fibres may cause pain and trigger central sensitisation in the spinal cord. Input from an inflamed nerve sheath may also cause pain and initiate changes in dorsal horn circuitry.

## **2.6 A Hypothesis for Symptoms in RSI**

On the basis of this review of minor nerve injury figure 2.3 outlines a hypothesis of the sequence of events leading to minor nerve injury in people carrying out intensive and repetitive tasks such as prolonged computer keyboard use.

- ① Minor changes in the neuronal environment caused by:
  - Long periods in constrained posture involving sustained muscle activity in the upper limbs
  - Possibly causing impairment of blood flow
  - Sometimes with direct and indirect pressure on nerves, e.g. wrist held in extension and resting on desk, elbow flexed and resting on chair arm
- ② Marginal impairment of neural mobility
  - Prolonged muscle contraction plus shoulder girdle and arm postures may increase stress and pressure on nerve
  - This causes further changes in local environment
- ③ Eventually get mechanical injury and inflammation
  - Nerve may be affected at several sites
  - Some loss of function may occur
  - But widespread degeneration does not occur
  - Reduction in axoplasmic transport can trigger changes at a distance
  - Inflammation may lead to nerve sheath fibrosis with further mechanical stress on nerve
- ④ Two sources of abnormal activity will develop
  - Ectopic firing of fibres within nerve
  - Activation of nervi nervorum
- ⑤ Abnormal input activates central pain circuits causing pain
  - If prolonged this abnormal input can cause central sensitization
- ⑥ Outcome is chronic arm pain from no obvious source

Fig. 2.3 A hypothesis for a neuropathic source of symptoms in RSI



## **Chapter 3:           Vibration sensory threshold testing**

### **3.1 Background to vibration sensory testing**

Changed vibration sense has been found in many examples of peripheral nerve dysfunction, for example, diabetic, toxic, uraemic, alcoholic and vibration induced neuropathies (Lindblom U, 1979, Lundborg G et al. 1992, Nielsen K, 1972, Kopple J et al. 1971, Hilz M et al. 1998, Lundborg G, 1987). Vibrotactile measurements are also considered a valuable diagnostic tool in the assessment of compressive neuropathies such as carpal tunnel syndrome, cubital tunnel syndrome and compartment syndromes (Bleeker M, 1986, Dellon, 1981, Lundstrom 1992, Phillips J et al. 1987, Lundborg G et al. 1992). Indeed Lundborg (1992) reported that altered vibration perception, particularly in the higher frequencies (250- 500 Hz), was the earliest clinical finding in peripheral compression neuropathy. Schwartz et al. (1983) consider vibration perception measurement to be a sensitive technique for diagnosing mild nerve pathology in clinically asymptomatic patients. While Schaumberg et al. (1991), recommended quantitative sensory testing for the longitudinal evaluation of patients at risk of subtle sensory dysfunction (e.g. cumulative trauma disorders).

Patients with RSI exhibit some signs of change to sensory nervous system sensitivity (Cohen 1992). However signs of slowed nerve conduction or changes in EMG activity have not been demonstrated. Such changes are not always apparent following minor nerve injury (Spindler,1990). Painful neuropathy, for example post herpetic neuralgia, can occur with symptoms of allodynia and hyperalgesia. However while raised thresholds on quantitative sensory threshold testing are commonly found, nerve conduction changes are not usually present (Nurmikko et al. 1990) The peripheral nerve is very sensitive to ischaemia , with changes in vibration perception threshold being

observed at pressures within the carpal tunnel of 40 – 50 mmHg. (Gelberman et al. 1983) . Rydevik et al. (1981), demonstrated impairment of intraneural blood flow at pressures of 20-30 mmHg. Capillary blood flow being reduced at 40 mmHg. A $\beta$  fibres (large diameter myelinated fibres) mediate the sensation of vibration. These fibres are considered to be the most vulnerable to ischaemia (Cosh 1953, Dellon1980). As large myelinated fibres they may be at most risk of oxygen depletion (Phillips et al. 1987). However mechanical compression, which will involve blood flow changes, effects nerve fibres depending on their position within the fascicle. Fibres positioned near the periphery being most affected. Dellon (1981), suggests that large axons are more affected by direct pressure than are smaller ones and that clinically, touch is the first sensation to alter following compression neuropathy. The earliest axonal change following nerve compression is displacement of myelin at the nodes of Ranvier and associated paranodal myelin damage (Neary 1975). Lundborg (1988), suggests that this is due to the narrowing of the axon that occurs at the node of Ranvier. These relatively narrowed points of the axon form a block to the free flow of axoplasm caused by the associated pressure gradient, causing displacement of the nodal axolemma and the myelin attached to it. In the absence of frank neuronal degeneration such changes to the nerve may affect impulse transmission.

We considered that measurement of vibration perception threshold in patients with RSI represented a more subtle determination of A $\beta$  sensory function than studies of nerve conduction velocity. Further we used suprathreshold vibration stimulation as a measure of subjects sensory response to non noxious suprathreshold mechanical stimulation. Allodynic and hyperpathic sensory responses have been described in patients with neuropathic disorders following non-noxious stimulation using various vibrametres (Lindblom U 1994, Wahren and Torebjork 1992).

### **3.1.1 Vibration Perception**

Measurement of vibration perception is dependant upon the integrity of the entire somatosensory pathway (Halonen, 1986). This includes components of both the peripheral and central nervous system.

### **3.1.2 Peripheral Nervous system**

Peripheral fibres that mediate the sensations of vibration, light touch and pressure comprise of are A $\beta$  caliber. These nerve fibers are myelinated, 5-14 $\mu$ m in diameter and have a conduction velocity of 25-75 m/s. The mechanoreceptor sensory units with A $\beta$  axons can be classified according to their adaptation properties to constant pressure stimulation and the characteristics of their receptive fields. There are two main kinds, rapidly adapting (RA) and slowly adapting (SA). ( See Fig 3.1)

### **3.1.3 Vibratory Stimuli and Sensory Units**

Rapidly Adapting mechanoreceptor has been used as a synonym for fast adapting (FA1 and FA11) afferent units. These mechanoreceptors respond with a steady stream of impulses only during a movement of the skin and not when the skin is held constant in a new position. Responses to vibration (0.5 – 400 Hz, 0.001-1.0 mm) have been recorded from single mechanoreceptive afferents from the glabrous skin in humans (Lundstrom 1986). FAI units fired at frequencies between 5 – 100Hz, and FAII above 50Hz.

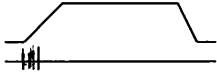
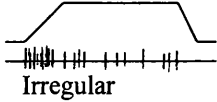
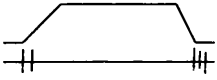
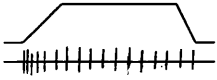
ADAPTATION			
Fast, no static response		Slow, with static Response	
<b>RECEPTIVE FIELD</b>  Small sharp borders	  Edge sensitive 26-91 m/s tap, flutter <b>FAI</b> Meissner	  Edge sensitive 32-82 m/s pressure <b>SA I</b> Merkel	<b>INNERVATION DENSITY</b>  Most dense at finger tips
Large graded borders	  vibration 34-61 m/s  <b>FA II</b> Pacini,	  Sensitive to lateral skin Stretch 34-55 m/s  may have spontaneous activity <b>SA II</b> Ruffini	More evenly distributed Throughout hand

Fig.3.1 Type and characteristics of mechanoreceptors found in glabrous skin of the human hand

Centre boxes show action potential discharges (lower line) in response to ramp and hold indentation of the skin. Centre boxes also show the conduction velocity and the sensations produced by intraneuronal microstimulation

Adapted from: Greenspan and Bolanowski 1996

These sensory units are excited by movement and code the velocity of movement as a frequency of discharge. The sensory terminals of FAII units are pacinian corpuscles, and FAI are Meissner's corpuscles.

#### Pacinian corpuscle (PC, FAII )

These have large receptive field with indistinct borders. They respond to high frequency sinusoidal vibratory stimuli, in a range of 50 – 1000 Hz with minimum thresholds in the region of 1µ m at approximately 300 Hz. They consist of large laminated structures (1mm long) with an onion like lamellar structure formed of non-neural tissue and an elongated nerve terminal at their centre. They are situated deep in the dermis or subcutaneously, and are more common in glabrous skin. These units show only a slight difference in density across the hand.

#### Meissner's Corpuscles (MC, FAI)

These have small distinct receptive fields and are encapsulated receptors lying in the superficial dermis of human glabrous skin. The receptor consists of helical layers of non-neural tissues oriented at right angles to the long axis of the corpuscle. Collagen fibres connect the distal receptor to the overlying epidermis and provide a mechanical link from the epidermis to the nerve endings in the receptor. These corpuscles are edge sensitive and only respond to vibration frequencies at a lower, but overlapping range compared to the PC units, from 5 – 100Hz. Along with SA I afferents (see below), FA I afferents have a large gradient of innervation, being most dense in the fingertips.

### Hair follicle receptors

These nerve endings are arranged in a circumferential array around hair root sheaths, beneath the sebaceous glands. Hair follicle units are rapidly adapting mechanoreceptors that discharge with hair movement and some demonstrate excellent response to vibration stimulation between 20-100Hz.

### SA units

Slowly adapting SA II receptors have a resting discharge and synchronised responses best in the 20 –100HZ range. They are sensitive to lateral skin stretch.

SA I units exhibit a large innervation gradient from the finger tips to palmer skin and are edge sensitive with small receptive fields. Unlike SA II units, in the absence of stimulation they do not demonstrate spontaneous activity. They will respond to vibration stimulation between 10-100Hz, producing a sensation of pressure.

In summary all of these units will respond to vibration stimulation at 100Hz, the frequencies commonly used for sensory vibration testing and the one employed by the Samedic AB vibrametre used in this study.

### **3.1.4. Central Nervous System**

Information from the mechanoreceptors is transmitted via A $\beta$  axons to the spinal nerves with cell bodies in the dorsal roots and enter the spinal cord as the medial bundle of the dorsal roots. In the dorsal horn they branch into fibres which a) terminate mainly in laminae III to V, with some PC units terminating in laminae VI of the dorsal horn and b) the largest fibres ascend in the funilculi gracilis (lower body) and cuneatus (upper part of body) of the posterior column. They terminate in the nucleus gracilis and cuneatus of the lower medulla. While the the dorsal columns are the key pathways for vibration

information some A $\beta$  fibres synapse in the dorsal horn and post synaptic cells signal via the antero lateral system. This can be demonstrated following cordotomy, a procedure where the spinothalamic pathway is interrupted on one or both sides to produce pain relief. As expected the patient becomes insensitive to pin prick, heat and cold but additionally touch sensation is reduced (Nathan et al. 1986).

The cells in the gracile and cuneate nuclei dorsal column nuclei, (DCN) send axons to the contralateral thalamus via the medial lemniscus. These cells receive input from RA mechanoreceptor units, PC units and SA1 units. Some may respond to just one class of afferent, and in some cases one afferent fibre can determine the responsiveness of the DCN cell. These cells have some ongoing background firing and inhibitory receptive fields usually adjacent to or surrounding the excitatory field.

Impulses are then conveyed via the internal arcuate fibres, decussating in the lower medulla, to terminate in the ventral posterior lateral nucleus (VPL) and posterior nucleus of the thalamus. Third order axons ascend from the VPL nucleus to terminate in the somatosensory areas 3b,3a, 1 and 2 of the cerebral cortex in the post central gyrus and in the secondary somatosensory system (SII). In these areas two distorted homunculus represent the somatotrophic organisation of the body, distorted as regions with high density of receptors (e.g lips, hands) having the largest cortical representation. The primary projection of cutaneous receptors is to area 3b, whereas area 3a is the primary projection area for joint and muscle receptors. One class of neurones, particularly in area 3b, respond to the temporal period of low frequency vibration(<100Hz) in the same range that excites Meisner's corpuscles. Next to area 3 is area 1 and here neurones receive convergent information from both cutaneous and muscle and joint receptor systems. Neurones within area 1 respond to higher frequency stimulation, those best processed by pacinian corpuscles. In area 2, lying posterior to area1, the convergence

is more marked and this region may be concerned with feature interaction. These SI areas project to the parietal association areas, firstly area 5 then area 7. These areas, receiving projections from other cortical sensory areas and visual, cutaneous and auditory stimuli, are involved in the cerebral processing of somesthetic afferent input. The anterior part of SII area is excited by tactile stimuli and comprises cells that respond to gentle mechanical stimulation (Robinson and Burton 1980). The posterior region of SII receives input from the posterior region of the thalamic nuclei, the neurones here are activated by stimuli with nociceptive information.

There are interconnections via the corpus callosum, between corresponding areas of the two sides of the cerebral cortex. SI receives input from SI of the other cortical hemisphere while SII has inputs from both SII and SI.

Positron emission (PET) studies in humans show that vibrotactile stimuli influence multiple cortical areas beyond SI and SII. Neurones in the insula, Ri area and 7b area increase their firing rate in response to vibrotactile stimulation (Coghill et al 1994).

Neurons within the central nervous system sometimes maintain a clear relationship with one group of afferents, i.e. they are mechanoreceptive or nociceptive specific. However within the dorsal horn there are signs of considerable convergence, for example, enlarged receptive fields. Other neurones have wide dynamic range properties (WDR) and receive information from several change types of afferent neuron i.e. A $\beta$ , A $\delta$ , C fibres. As a consequence of excitatory or inhibitory modulation and stimulus strength they demonstrate considerable plasticity of response (Weinberger 1995, McMahon 1993).



### 3.2 Measurement of Vibration Threshold

Goldberg and Lindblom (1979) demonstrated methods for the measurement of vibration threshold (VT) using skin deformation measured in  $\mu\text{m}$ . The psychophysical threshold normative values for vibratory perception have been evaluated. Vibration thresholds in the hand averages between 0.20 – 0.40  $\mu\text{m}$  <sup>at 100Hz</sup> for normal healthy subjects aged between 20 – 49 years ( Hilz 1998, Goldberg and Lindblom 1979,). Hilz (1998), used the Somedic AB vibrometre, Golderberg (1979) an earlier version of this device. With both studies vibration frequency was constant at 100Hz, with probe pressure contact maintained at 550g. Doezie, et al (1997), used a multiple frequency vibrometer and while probe pressure was kept constant magnitude is not stated. However in their control group , (aged between 25-61; mean 38 year) an average threshold of 0.30  $\mu\text{m}$  was recorded at 125 Hz.

#### 3.2.1 Factors that may modify Vibration threshold

##### Age

Increasing age has been associated with a decrease in vibration sensitivity (Verillo 1979). However this was apparent only above the 5<sup>th</sup> decade (Hilz 1998).

##### Gender

No significant gender differences have been noted below the age of 50 (Hilz 1998). Above this age higher thresholds have been noted in men. This has been explained by age related degeneration of the peripheral nervous system said to occur earlier in men than in women (Halonen 1986).

### **Frequency of vibrating stimulus**

Perceived intensity of vibration varies with vibration frequency ( Verillo 1962, 1971, Goff 1967). Below 250 Hz the stimulus presented must be at a greater amplitude to equal the perceived intensity at higher frequencies. The range from 200-300Hz reflects the optimum range for stimulation of the Pacinian receptor system. Lundborg (1992) reports that elevated threshold at higher frequencies (250-500 Hz) are the first sign of sensory dysfunction.

### **The application pressure of the probe**

Changes in probe application pressure change threshold perception, with an increase in pressure causing significant threshold reduction at frequencies of 50- 125 Hz (Verillo 1962, Goldberg and Lindblom 1979). Hagander et al. (2000) found that testing at 100Hz under 30-50g/1.22cm<sup>2</sup> pressure gave equal vibration thresholds. However thresholds were higher when tested under 100g/1.22cm<sup>2</sup>. They concluded that the difference was clinically negligible. Testing with the Somedic AB vibrometre allows the operator to rest the weight of the hand held stimulator on the surface being tested and for this pressure to be calibrated and standardised. While this is convenient for ease of use, the weight of the stimulator is 550g and care needs to be taken that this is not uncomfortable for the subject.

### **Probe contact surface area**

The size of the vibrating probe will be significant if spatial summation is important. Verillo (1962), reported that at frequencies above 40 Hz thresholds fall by 30% for every doubling of the contact area (<10mm<sup>2</sup> – 500mm<sup>2</sup>), later confirmed by Hollins et al. (1990).

### **Test sites studied**

Differences between test sites studied, bony area compared to soft tissue, will also affect vibration perception threshold. Bone sites such as the tibia causing a decrease in sinusoidal amplitude (Goldberg and Lindblom 1979). However this dampening effect disappeared at high frequencies of 250-500Hz (Era and Hanninen 1987). The Somedic AB vibrametre used for our studies has a feedback mechanism from the vibrating probe that maintains the vibration amplitude when testing over different surfaces.

### **Test protocol**

In our study vibration threshold (VT) was determined by the method of limits (Goldberg and Lindblom 1979). VT was calculated as the average of three vibration appearance threshold measurements and three disappearance thresholds measurements. The method of limits has been shown to produce the same variability in results as the adaptive forced choice method (Muijser H et al 1986) and was found to be more reliable, and less time consuming than the forced choice method (Gerr and Letze 1988).

### **Co operation of the subject**

Trial tests to determine subject co-operation and carrying out tests in a quiet environment assist with consistency of results.

### **Presence of painful symptoms**

The presence of painful symptoms that may distract the subject may be thought to influence VT. In most cases careful limb positioning can reduce painful symptoms. However Checkosky et al (1996), found no change in threshold in the presence of pain related to carpal tunnel syndrome.

## **Ambient Temperature and Skin Temperature**

Halonen (1986) found that skin temperature within a range from 20 – 40 °C had no effect on VT at 100- 125 Hz as subsequently did Claus et al. (1993). However skin temperature above 32°C is reported to lower thresholds while a skin temperature of 15°C to elevate them ( from Greenspan and Bolanowski 1996). Hiltz (1998), recommends that tested extremities should be warmed when skin temperature is below 25°C. Gerr and Letze (1993) suggest that VT is not affected by skin temperature over the range usually encountered at normal ambient room temperature.

### **3.2.2 Other factors that may modify vibration threshold**

#### Height

This has been found to be positively correlated in two studies, both of which measured VT at the ankle (Wiles et al. 1991, Era et al 1986 as reported in Schwartz B and Kilma 1995).. Hiltz et al. (1998), found no correlation between height and threshold. Skov et al. (1998), found that for finger threshold, height was not an important factor.

#### Lateralised sensitivity

Rhodes (1981), Gerr et al (1990) found a difference between VT and left and right hand , with increased vibration sensitivity noted on the non-dominant side. However these findings are exceptional and other studies have not found hand dominance to be a factor (Hiltz M et al. 1998, Halonen 1986, Bloom et al (1984).

#### Adaptation to the stimulus

Adaptation to the vibration stimulus may occur and result in vibration threshold shifts. Lundstrom (1986) showed, via single fibre recording in the median nerve, that the firing frequency of mechanoreceptors decreases as a result of ongoing vibration. Hollins et al.

(1990) found, at frequencies above 50 Hz, an exponentially increasing threshold adaptation over a time constant of 1 – 2 minutes, on the pad on the index finger. However the adapting stimulus was in the range of 30-70 $\mu$ m considerably larger than the range used to detect vibration thresholds on the hand(0.3 - 3.0  $\mu$ m.) Van Dijk et al. (1991) recorded a rise in vibration disappearance threshold following measurement of vibration appearance threshold. However disappearance threshold was only elevated following pre vibration stimulus of 1.2  $\mu$ m and 3.2 $\mu$ m for one minute. In this study mean vibration perception thresholds were 0.29 $\pm$ 0.19 $\mu$ m. The pre-test stimulus was thus approximately greater than threshold by a factor of 4 and 11 respectively. This test protocol differs from the recommended protocol where vibration disappearance threshold is directly measured following the vibration appearance threshold measurement.

### **3.3 Summary**

Vibration perception testing has been shown to be a sensitive technique for evaluating even mild neural pathology. Once factors such as probe area, contact pressure, subject co-operation, standardised test sites and familiarity with the equipment are controlled for, repeatable results can be obtained. Repeat tests with intervals of one day to some weeks show good repeatability,  $\pm$  20% (Fagius and Wahren, 1981, Rosecrance et al 1994).

Our study used the Somedic AB Vibrametre (Somedic, Sweden). Frequency is fixed at 100 Hz and probe contact pressure maintained at 550g (the weight of the hand held stimulator).

## Chapter 4:

### Experiment 1: Vibration sense in the upper limb in patients with repetitive strain injury and a group of at-risk office workers

#### 4.1 Subjects and methods

Subjects were excluded from the study if they suffered systemic illness, connective tissue disorder or had experienced obvious trauma to the upper limb. The office workers (n=29) were recruited from a large publishing firm. Their occupations included secretary, journalist, sub-editor and editor. Overall length of time using display screen equipment (DSE) and proportion of time currently spent using DSE were assessed by use of a questionnaire. If they were experiencing symptoms in their upper limb they were asked to record these on a body chart. Time absent from work and treatment received were also noted.

Patients (n=17) were recruited from various physiotherapy clinics, both private and associated with the National Health Service. All subjects in this group had been diagnosed as suffering from RSI by their GP or Consultant. Patients were interviewed and information obtained regarding the nature, site and duration of their symptoms. At the time of symptom onset their occupations involved intensive keyboard use as legal secretaries, journalists, and data input clerks.

Control subjects (n=27) were recruited from university students and teaching staff at a secondary school. None of the control group intensively used DSE, although most were familiar with its operation and used it occasionally. The age range and male:female ratio were approximately matched to those of the office worker and patient groups (see Table 4.1). Subject age range was restricted to between 20 –55 years. The study was

approved by University College London, Middlesex Hospital Ethics Committee. All subjects gave informed consent.

#### **4.1.1 Clinical examination**

All subjects underwent a clinical examination. This included assessment of the range of movement of the cervical spine and upper limbs. Signs of tenosynovitis, epicondylitis and sympathetic dysfunction were specifically looked for. Sensory changes were ascertained by testing of sensitivity to pin prick and light touch. Tendon reflexes were examined and muscle power assessed using the Oxford scale (Brain 1976). Existing arm pain was rated by using a visual analogue scale (VAS), where 0 represents no pain and 100 represents worst possible pain.

#### **4.1.2 Vibration test methods**

The Vibrametre (Somedic AB, Stockholm, Sweden) used in our studies complied well with the technical requirements of VT testing. This hand held vibrametre allows for the direct measurement of amplitude of the vibrating probe and controls for the application of pressure. This was kept constant, via a monitor on the control unit, at 550g (the weight of the stimulator). The vibrating probe, 13 mm in diameter, vibrates at a constant 100 Hz (twice AC frequency). The vertical peak-to-peak amplitude of the probe is measured by an accelerometer and is displayed digitally in  $\mu\text{m}$  on the control unit. (See Fig 4.1).

Previous studies have established the validity and reliability of this equipment (Goldberg and Lindblom 1979). Hiltz et al. (1998) considered that the high reproducibility of their results was mostly due to the technical compliance of the Somedic vibrameter, (measurement of amplitude in  $\mu\text{m}$ , pressure application monitor). All subjects were naive to the test procedure.

## Procedure

All subjects were examined and measured individually in an air conditioned room between 9.30a.m. and 4.00 p.m. Room temperature was maintained at 21-22°C. Subjects were allowed to rest prior to testing. Each subject was seated comfortably with arms supported and without sight of the vibrametre display.

Prior to vibration threshold testing each subject was familiarised with the test procedure by trials using the stimulator over the radial or ulnar styloids.

Vibration threshold (VT) was determined by the method of limits (Goldberg and Lindblom 1979). VT was calculated as the average of three vibration appearance threshold measurements and three disappearance threshold measurements. Readings were taken at three sites (i) dorsum 5<sup>th</sup> metacarpal (ii) dorsum 2<sup>nd</sup> metacarpal, (iii) volar aspect of the 1<sup>st</sup> and 2<sup>nd</sup> metacarpal. These test sites correspond to areas of skin supplied by the ulnar, radial and median nerves respectively. The average of the appearance threshold and disappearance threshold measurements were calculated as a measurement of VT.





Fig 4.1 The Somatic AB vibrametre

Following the initial testing the subjects were then asked to type on a computer keyboard for 5 minutes. All the office workers were given a piece of copy to work from and were encouraged to make use of copy stands and ensure that their seats were comfortably adjusted. They were requested to type at normal speed. Control subjects were asked to imagine that they were experienced typists and type at a steady speed. On average 50 words per minute was maintained. Patients typed as fast and as long as they could, up to a maximum of 5 minutes. Vibration threshold tests were then carried out, as previously described, following a rest period of 5 minutes.

Finally the subjects response to suprathreshold vibration stimulation was tested. This was examined over the soft tissues of the forearm. For patients and office workers with symptoms the non symptomatic or least symptomatic side was tested first. All subjects were instructed to report any sensory experience other than vibration. The stimulation was increased either until tolerance or maximum amplitude (400  $\mu\text{m}$ ) of the machine was reached. The tolerance levels and any sensory changes were noted.

## **4.2 Statistical analysis**

This was performed using SPSS Windows software. Non parametric (Chi-Square, Mann-Whitney, Kruskal-Wallis) and repeated measures of analysis of variance were performed. Critical P value 0.05

## **4.3 Results**

### **4.3.1 Repeatability**

Repeatability measured on five subjects made by two examiners (including the author), from two recordings made at a one weekly interval showed a SD of 0.06 $\mu\text{m}$ , subject average of  $\pm 15\%$ .

### 4.3.2 Clinical examination: Office Workers

We tested 29 subjects, 21 women and eight men (see Table 4.1). Mean age was 30 years, range 20-55 yrs. Occasional pain was reported by 60% of this group, predominately described as aching over the wrists, hands and forearms, although some subjects also reported cervical spine and shoulder girdle aching. At the time of testing only three subjects reported current symptoms. On assessment of VAS, none reported pain greater than 40%. Clinical screening found only one subject to have specific signs of tissue inflammation, with signs of osteoarthritic changes at the 1<sup>st</sup> metacarpal joint.

### 4.3.3 Clinical examination: Patient group

We tested 17 subjects, 14 women and 3 men. Mean age was 36 years, range 24-53 yrs. Average duration of symptoms was 2.8 years (range 5 months- 10 years). Nerve conduction studies in the 8 cases where this was performed were reported as normal. Two patients had undergone bone scans, in one this showed demineralisation of both the radial and ulnar styloid processes. Standard clinical neurological tests for muscle power and tendon reflexes were normal. Sensory testing to light touch demonstrated in 10 subjects areas of hypoaesthesia and <sup>in 10 patients</sup> allodynia to light touch in 16 subjects. Areas of hypo and hyperalgesia frequently co existed in the same patient. A total of 14 patients reported areas of paraesthesia, predominantly over the hands and fingers with a non-dermatomal organisation. No sign of tenosynovitis, epicondylitis or other soft tissue inflammatory condition was discernable using standard orthopaedic examination procedures. See Table 4.1 for patient details.

#### 4.3.4 Clinical examination: Control subjects

We tested 27 subjects 21 women and 6 men. Mean age was 33 years, range 18-55 yrs. None currently reported symptoms. Clinical screening did not demonstrate sign of any upper limb musculoskeletal disorders.

Table 4.1 Summary of characteristics of the three groups studied

	Number	Male / Female	Average Age	Age Range	Number currently with arm pain
Controls	27	6/21	33	18-55	0
Office workers	29	8/21	30	20-55	3
Patient	17	3/14	36	24-53	17

### 4.3.5 Vibration testing before keyboard use

Base line right and left side VT data were averaged and compared by group, as shown in Fig 4.2.

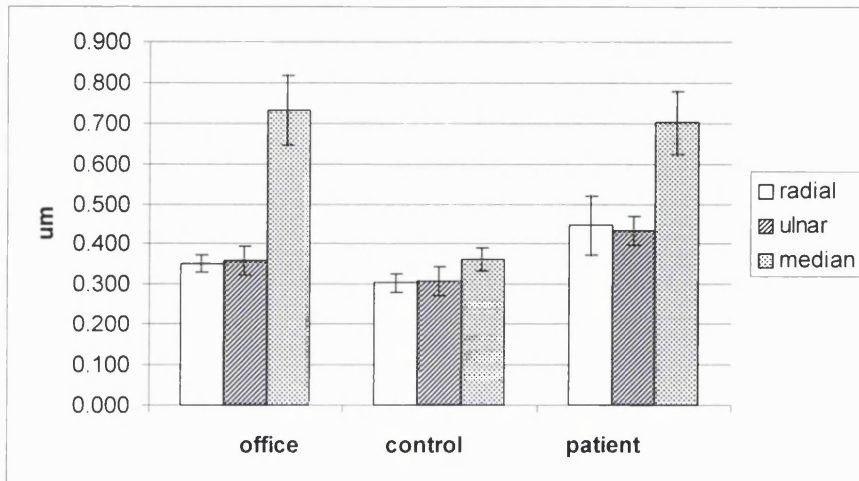


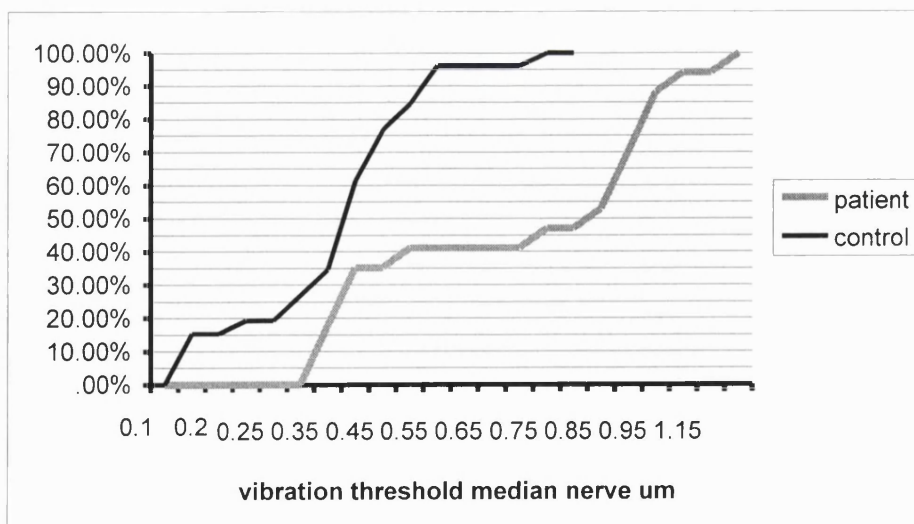
Fig 4.2 Baseline averaged VibrationThreshold (VT) data for all groups

In the control group all areas innervated by the radial, median and ulnar nerves on both hands showed similar vibration thresholds. In contrast in both the patient and office workers groups the vibration perception thresholds of skin innervated by the median nerve were approximately twice normal values. On average median nerve area vibration threshold for the office worker group was  $0.72 \pm 0.086 \mu\text{m}$ , for the patient group the average was  $0.67 \pm 0.071 \mu\text{m}$ . The control group average for vibration threshold for the median nerve was  $0.36 \pm 0.27 \mu\text{m}$ . Kruskal-Wallis 1-Way Anova showed that the patient and office worker groups were significantly different from the control group ( $p < 0.01$ ), but did not differ significantly from each other.

Threshold values for the ulnar nerve also differed in the patient group compared to both control and office worker groups. The patients average values for the ulnar nerve area

vibration perception threshold were  $0.44 \pm 0.03 \mu\text{m}$ , control average  $0.310 \pm 0.022 \mu\text{m}$  and office worker average  $0.36 \pm 0.03 \mu\text{m}$ . Analysis of variance demonstrated that in the patient group ulnar area vibration threshold differed significantly from both the control and office worker averages ( $P < 0.05$ ), but that control and office groups did not differ significantly from each other. Control, office and patient average threshold values for the radial nerve were  $0.30 \pm 0.02 \mu\text{m}$ ,  $0.35 \pm 0.02 \mu\text{m}$ ,  $0.41 \pm 0.38 \mu\text{m}$  respectively. Kruskal-Wallis 1-Way Anova for the radial nerve vibration threshold by group was not significant. Initial analysis for side effects demonstrated no significant effects. Overall ANOVA by age group showed a small trend for only the radial nerve values ( $f = 4.802$  sig  $f = .004$ ). While there are clearly significant trends between the groups for threshold values in the median nerve area there is also some overlap. Cumulative percentage frequency for the control group average median nerve data, prior to keyboard use, demonstrates that at the 96% cumulative frequency level,  $0.55 \mu\text{m}$  threshold value represents the value above which threshold results may be considered significantly raised. (See Fig 4.3).

Fig. 4.3 Cumulative frequency histogram of base line averaged median nerve area VT for the patient and control groups



#### 4.3.6 Vibration threshold following keyboard use

The control subjects demonstrated a small fall in vibration threshold for all areas. For the median area average values fell from  $0.36 \pm 0.027 \mu\text{m}$  to  $0.33 \pm 0.025 \mu\text{m}$ . Similarly for the radial area  $0.30 \pm 0.023 \mu\text{m}$  to  $0.27 \pm 0.02 \mu\text{m}$  and the ulnar area  $0.31 \pm 0.02 \mu\text{m}$  to  $0.27 \pm 0.02 \mu\text{m}$ . All of these falls in vibration threshold were significant (analysis of variance  $P < 0.05$ ). No change was observed for the office workers. However in the patient group threshold in the median area increased on average, from  $0.67 \pm 0.071 \mu\text{m}$  to  $0.92 \pm 0.12 \mu\text{m}$ , ( $P = 0.006$ ). This rise was most apparent on the right side, from  $0.70 \pm 0.07 \mu\text{m}$  to  $1.075 \pm 0.16 \mu\text{m}$  ( $P < 0.01$ ). The left side increased only from  $0.63 \pm 0.07 \mu\text{m}$  to  $0.77 \pm 0.11 \mu\text{m}$  a change that was not significant (data not shown). See Fig 4.4 for right side median nerve area VT data post keyboard use. Values for the radial and ulnar areas did not change in the patient group. All patients except two were right hand dominant.

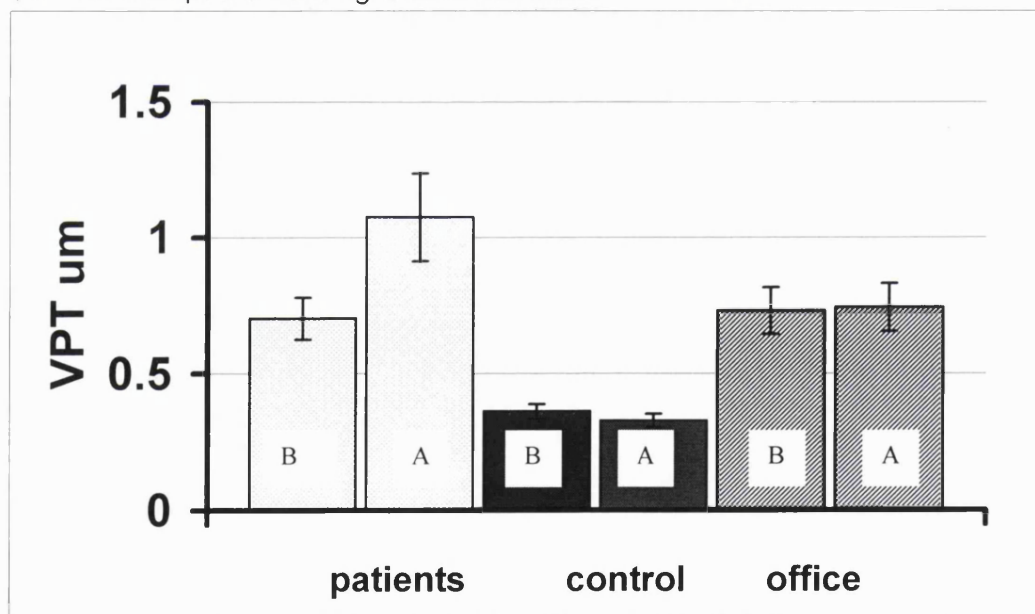


Fig 4.4. Values for vibration perception threshold for the right median nerve before and after typing

Key: (B) before and (A) after keyboard use.

#### **4.3.7 Vibration Tolerance**

Both control and office worker subjects tolerated maximum output of the vibrametre (400  $\mu\text{m}$ ) over the soft tissues of their forearms. No subject reported any sensation other than a strong buzzing. In contrast 14 of the 17 patients could not tolerate vibration within the vibrameter range on one or both arms. This reduced tolerance was most apparent over the dominant arm in this group usually the right side. Those affected described painful sensations in the forearms and hands, 3 patients experienced painful sensations at some distance from the stimulation site. Five subjects experienced painful sensations at low output of the machine, while nine subjects had reduced tolerance at or near maximum output of the machine. All of those affected except one who was left hand dominant had reduced tolerance over their right dominant upper limb. A bilateral reduction in tolerance was shown by six subjects.

#### **4.4 Discussion.**

Vibration threshold was raised in both the office worker and patient groups. This is consistent with change in function of the large sensory fibres (Lang 1995, Lindblom U, Goldberg JM 1979 Lundborg et al 1992). The effects were most apparent in the median nerve, although ulnar nerve thresholds were also slightly elevated in the patient group. Patients, but not the office workers, showed a work related exacerbation, with median nerve thresholds rising significantly following keyboard use. In addition the patient group show reduced tolerance to suprathreshold, but non noxious, vibration stimulation. This lack of tolerance was associated with pain or other unpleasant sensations, indicating a change in the way non noxious sensory input is processed. Greater threshold changes and decreased tolerance were more apparent on the dominant side. This may indicate increased fascicular damage related to increased use of the dominant side. RSI patients



have been reported to show a reduced flare response following the application of capsaicin (Helme 1995), a change that is consistent with small sensory fibre loss. Changed autonomic responses have also been reported in RSI patients (Cohen 1992) and were present in several of our patients. Nerve conduction studies may appear normal in the presence of minor fascicle damage and such studies do not detect damage to small sensory nerve fibres (Spindler and Dellon 1990).

Overall, the RSI patients appear to have symptoms and objective signs of a minor neuropathy. Clear changes are apparent in vibration threshold of the median nerve area in a group of office workers who intensively use computer equipment.

This finding indicates that quantitative measurement of vibration threshold may be useful in patient assessment and may also provide a means of detecting early neural deficit in subjects who intensively use computer keyboard equipment. However while there are clear group trends there was considerable overlap in vibration threshold between the groups studied. From this data, at the 96% confidence interval, vibration threshold above 0.6µm would indicate a clearly abnormal threshold response.

#### **4.5 Criticism of Methodology**

1. This study may have been subject to observer bias since blinding to subject status was not possible. However, as part of an ongoing study on neurophysiological measures of nerve function in RSI patients, vibration threshold is being measured in a single blind fashion. In this study baseline VT is measured (without keyboard use) using the described methodology, while clinical screening is being carried out by a research assistant. Results so far indicate a similar pattern of VT to those found in this study. RSI patients (n=31) average threshold in the median nerve area  $0.63 \pm 0.05$ m, office workers

(n=14) average threshold  $0.53 \pm 0.03 \mu\text{m}$ ., control subjects, average threshold  $0.38 \pm 0.01 \mu\text{m}$  (n=21).

2. This methodology gives no indication where dysfunction in the neural pathway occurs. The observed change to VT may be the result of changed central processing. However, if this were so the expectation would be for an overall change in VT whereas these results clearly indicate that function of the median nerve is the most severely affected. **The results of this study have been published (Greening J, Lynn B 1998).**



## Chapter 5: Nerve Movement

As previously described, tests of upper limb neural mobility frequently produce painful responses in patients with RSI. The role of nerve movement in the production of painful nerve entrapment syndromes has not been extensively explored. Yet a clinical test of nerve movement in the lower limb, the straight leg raise (SLR), was first described by Lasegue in 1864, and is frequently used in the diagnosis of sciatica caused by lumbar disc lesions.

Nerves are dynamic structures, able to move several centimetres in response to changes in limb position. Extraneural gliding occurs in association with intraneural gliding of the fascicles in relation to each other. Nerves exhibit elastic and viscoelastic behaviour (Millesi et al. 1990). Under tension a nerve rapidly elongates as slack is taken up in the nerve trunk and fascicles. The normal undulation of nerve fascicles disappears as fibres straighten. As the nerve elongates cross sectional area is reduced. With continued nerve stretch a critical point is reached where conduction is blocked before any morphological changes can be detected (Lundborg 1988). These "tension" lesions correspond to Lundborg's description of physiological conduction block: type (a) local conduction block due to intraneural circulatory arrest with no axonal degeneration, which on release of tension / compression is immediately reversible, and (b) local conduction block associated with intraneural oedema but little or no neural degeneration that is reversible within days or weeks. With increased tension the nerve approaches its elastic limit to a point where axons rupture inside their still intact endoneurial tubes (Haftck 1970). Following this lesion axonal regeneration is required for recovery.

Cadavric studies have measured longitudinal movement of the peripheral nerves in the upper limb. Wilgis and Murphy (1986), observed movement of the median and ulnar nerves at the wrist to be 14.5 mm and 13.8 mm respectively, during flexion and extension at the elbow. Wright et al. (1996) measured both nerve excursion and strain of the median nerve in 5 cadavars. Both proximal and distal movements of the median nerve were demonstrated to occur in a predictable manner with movement of the shoulder, elbow and wrist. Composite movements of shoulder abduction 30 degrees, wrist extension 60 degrees and elbow flexion of 90 degrees produced maximum strain and distal excursion of the median nerve of <sup>23</sup>15 mm with a tensile strain of 18 %. Interestingly this upper limb posture is similar to the position adopted when using a computer keyboard. Overall, full movement of all the upper limb joints in this study identified a minimum of 30 mm of median nerve movement. The adaptation of nerves to changes in limb length is possible if nerves can move relative to surrounding structures and if fascicles can move relative to each other.

### **5.1 The consequences of restricted nerve mobility**

Normal neural gliding may be impaired following frank nerve compression. However, inflammation of the nerve sheath, following relatively minor nerve compression, can lead to fibrosis and adherence to adjacent structures (Sommer et al. 1993; Mosconi et al. 1996). Fibrosis either of extraneural and / or intraneural structures will impair normal neural gliding (Lundborg 1988). Reduced median nerve mobility at the carpal tunnel during finger flexion (Nakamichi and Tachibana 1992) has been observed in carpal tunnel syndrome and restricted median nerve movement been suggested as a cause of recurrent carpal tunnel syndrome (Wright et al. 1996).

Following loss of normal gliding mechanisms the subsequent traction effects on nerve segments may have important consequences for blood supply. Traction forces on rabbit tibial nerve producing strain lengthening of only 6-8% have been shown to

impede blood flow, while length changes of 15% to arrest neural blood flow (Remple et al. 1999, Lundborg and Rydevik 1973). While nerves are able to move freely during limb movement, tension within the nerve trunk is likely to be distributed over the entire nerve length. A pathological increase in neural tension could occur during physiological arm movements when a segment of nerve loses mobility for example, following nerve sheath fibrosis and adherence to surrounding structures. In this circumstance, tension within the nerve is unlikely to be dissipated and cause a segmental increase in nerve tension and change to neural blood flow. In this situation physiological ranges of limb movement may cause pain and paraesthesia. The loss of a nerve's ability to glide may also render it more likely to be exposed to compressive and irritative effects from closely related structures.

## **5.2 Clinical tests of nerve movement**

Several tests of nerve mobility in the upper limb have been suggested (Butler 1991). These are based on anatomic observations, in vitro studies, for example, Wilgis and Murphy (1986); Millesi et al. (1990), and one in vivo study (McLellan 1975). Butler 1991 described the "upper limb tension test" (ULTT1), as a mechanical test of median nerve and brachial plexus mobility. This test involves passive combined shoulder abduction, forearm supination, elbow extension and wrist extension to mechanically "tension" the brachial plexus and particularly the median nerve (see Fig. 5.1 ). During the test the range of elbow extension is evaluated while the arm is held in a 100° shoulder abducted position with the wrist extended. Evidence from cadaver studies has shown this test to be a sensitive and specific test for applying tension to the median nerve and the medial and lateral cords of the brachial plexus (Kleinrensink et al. 2000). The normative symptom response to the ULTT1 has also been studied (Kenneally et al. 1998). From the results of these tests, i.e restricted range of movement and painful responses, clinical diagnosis and treatment programs are formulated (Byng 1997). La Ban et al.(1986) described the median nerve stress

test. This test, involving extension of the supinated wrist and distal interphalangeal joint of the index finger, was reported to produce pain in the distal anterior forearm in 18 of the 20 patients with electrodiagnostic evidence of carpal tunnel syndrome. Anatomic and one operative observation have shown that greater excursion of the median nerve is produced by hyperextension of the index compared to the middle and ring fingers (La Ban 1989). The median nerve stress test has been examined in a blind comparison with electrodiagnostic tests for predictive power in cases of suspected carpal tunnel syndrome (Kaul et al. 2000). Sensitivity was 50%, specificity 59%, and positive predictive power 61%. The conclusion was that the median nerve stress test lacks utility in predicting electrodiagnostic test results. However, whilst electrodiagnostic tests are considered the "gold standard" for diagnosis of carpal tunnel syndrome, a diagnosis of carpal tunnel syndrome is frequently made on results of clinical tests and symptom presentation only. Nakamichi and Tachibana (1995) used ultrasound imaging to investigate median nerve sliding during passive flexion and extension of the index finger in patients with carpal tunnel syndrome. A significant restriction of nerve sliding was observed compared to control subjects. Although the wrist was not extended during their experimental procedure, index finger extension in the supinated wrist position forms part of the median nerve stress test as described above.

Compared to the median nerve stress tests, the ULTT1 has the potential to impose greater longitudinal strain on the median nerve since both proximal and distal joint movement is involved. Bay et al. (1997) looked at median nerve movement in a cadaver study during finger flexion in wrist flexion and extension positions and suggested that median nerve stretch and friction forces plus fascial tethering should be considered in the pathomechanics of CTS.

As previously mentioned tests of upper limb neural mobility frequently produce painful responses in patients with RSI. Following our initial experiments demonstrating elevated vibration thresholds in the median nerve distribution in patients with RSI, we decided to make a quantitative study in these patients of median nerve mobility at the carpal tunnel using magnetic resonance imaging.



B

Fig 5.1. Upper limb tension test 1: arm positions for testing.  
(A) start position for arm, (B ) final position of arm



## **Chapter 6:       Magnetic Resonance Imaging and the carpal                           tunnel**

### **6.1   Magnetic resonance imaging (MRI)**

MRI is a non invasive method of imaging anatomy in any plane with no radiation risk to the subject. One of the advantages of MRI over other imaging modalities is its ability to obtain good soft tissue discrimination.

The MRI signal depends on the movement of a magnetic field. Magnetic field strengths are measured in Tesla (T). Most MRI units operate from 0.2T to 2T. The charged particle in MRI that produce images is the hydrogen nucleus. Since the hydrogen nucleus has a single proton which has a fairly large magnetic moment. The magnetic moment of each nucleus has vector properties, i.e. has size and direction. When these nuclei are positioned in a strong magnetic field the magnetic moments of the hydrogen ions align themselves with the external magnetic field. Low energy nuclei align themselves in parallel to the external field and are termed spin up nuclei, those of high energy align themselves anti-parallel and are called spin down. Increasing the strength of the magnetic field increases the number of nuclei in the spin up position. The effect is to produce a net magnetic vector that is used in clinical MRI. The net magnetic vector (NMV) is larger in high field MRI than at low field strengths.

Hydrogen nuclei making up the NMV are spinning on their own axis. The external magnetic field produces an additional spin so that nuclei follow a secondary circular path around the external field. This effect is called the precession path and the speed at which precession takes place is called precession frequency. The precessional frequency is governed by the Larmor equation:

precessional frequency = external magnetic field strength x gyro-magnetic relationship  
(the angular motion and magnetic motion of each MR active nucleus).

The application of a radio frequency (RF) band of electromagnetic radiation at the exact frequency of oscillation of the hydrogen nuclei delivers more energy to this system. This effect is called resonance. The absorption of energy causes an increase in the number of spin down nuclei causing an increase in energy difference between the two hydrogen nuclei population (spin up and spin down).

Resonance thus produces a movement of the NMV out of alignment with the external magnetic field. The new angle of the NMV is called the flip angle, the magnitude of which depends on the amplitude and duration of the RF pulse. In practice the flip angle is 90 degrees. A transverse magnetic field now exists in which the magnetic moments are in phase and in the same place on their precessional path around the external magnetic field. As a result of resonance the NMV induces a voltage in a receiver coil. Signal is produced when the moving NMV crosses the coil. The magnitude of the signal depends on the amount of magnetism present in the transverse plane.

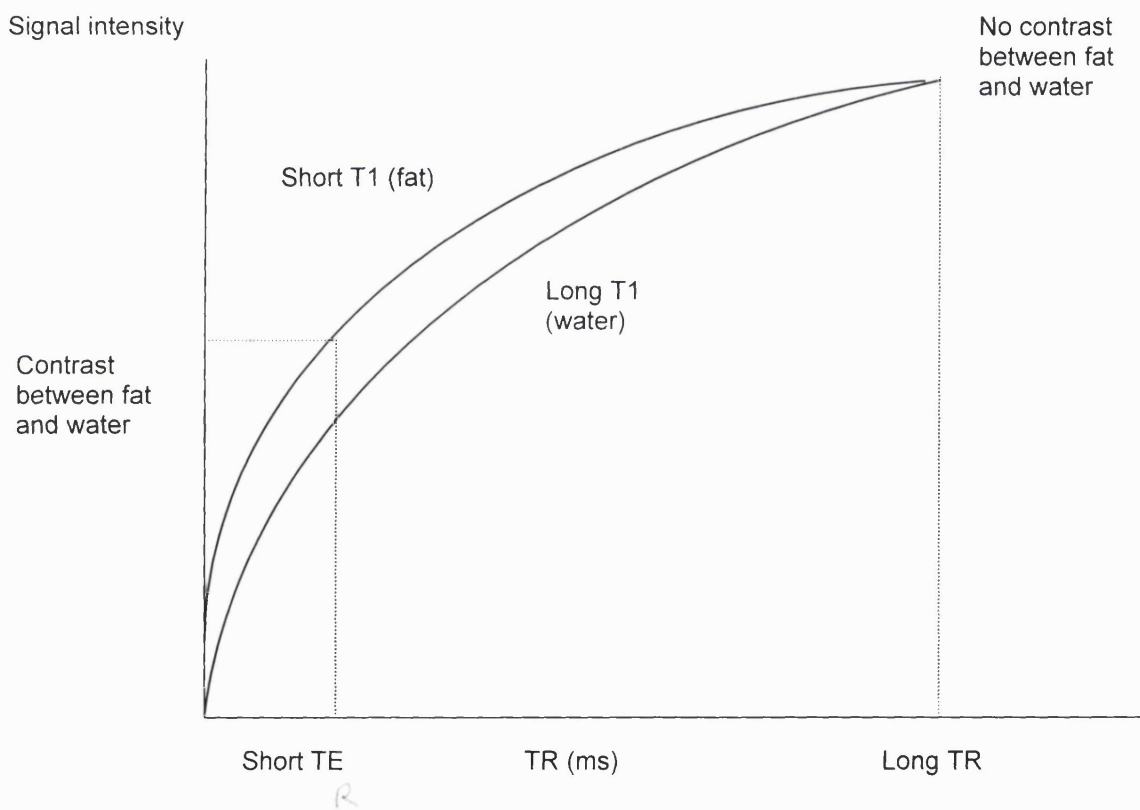
When the RF pulse is turned off, the NMV is again influenced by the external magnetic field and attempts to realign with it. To do this the hydrogen ion nuclei lose energy, a process called relaxation. Longitudinal magnetism now increases (called T1 recovery) and at the same time but independently magnetism in the transverse plane decreases (T2 decay). Timing parameters of the pulsed RF (repetition time TR), measured in milliseconds determines the amount of T1 recovery that has taken place. The echo time (TE) represents the time from the application of the RF pulse to the peak of the signal induced in the receiver coil. TE determines how much decay of the transverse magnetism is allowed before the signal is read. TE controls the amount of T2 recovery

that has occurred. The application of RF pulses at different repetition times and received signals at pre determined echo times produces the contrast between different tissues in MR images.

Contrast can be produced because different tissues produce different amounts of transverse magnetism. In clinical MR the two extremes are fat and water. In fat the hydrogen is linked to carbon which allows the electrons to protect the hydrogen nucleus from the effects of the external magnetic field. The Larmor frequency of hydrogen in fat is lower than hydrogen in water. Hydrogen in fat loses transverse magnetism more rapidly than water and therefore loses transverse magnetism faster. The T1 recovery in fat is also faster than that of water, and fat hydrogen nuclei regain longitudinal magnetism quickly. Manipulation of these different characteristics between fat and water allows for image contrast between them. A T1 weighted image is one where the contrast depends on the differences in the T1 times between fat and water. Because TR controls how far T1 recovery occurs before the next RF pulse. To achieve T1 weighting TR must be short enough so that neither fat and water have sufficient time to regain all longitudinal magnetism of the external magnetic field (see Fig.6.1).

T2 weighting allows contrast depending on the different T2 times between fat and water (see Fig 6.2). To achieve T2 weighting the TE must be long enough to give both fat and water time to decay. For T1<sup>2</sup> weighting the TE must be long. In T1 weighted images fat appears bright and water dark. In T2 weighted images the reverse is true and these parameters can be used to differentiate between different tissue components.

Fig. 6.1 T1 differences between fat and water



Images can be further refined by the use of RF echo sequences to nullify the signal from fat or water or reduce the confusing signal obtained from flowing nuclei (as in blood vessels). These protocols employ the use of pre-saturation RF techniques so that no transverse magnetism of particular tissue nuclei occurs in the predetermined image slices. The trade off in all of these protocols is the amount of magnetic field the patient is exposed to and the time required to obtain high quality images.

### Field of View

This is determined by the application of different gradients to the magnetic field. These either subtract or add to the external magnetic field relative to its centre and therefore the precessional frequency of nuclei along that gradient can be predicted. This is called spatial encoding and allows images to be obtained in different planes. (See Fig 6.3). A specific slice within this field can also be selectively excited by transmitting a RF pulse at the same Larmor frequency along the axis of the applied gradient, allowing imaging slice selection in the coronal, sagittal or oblique axis planes. The thickness of a slice can also be manipulated by altering the gradient slope. The steepness of the applied gradient determines the size of the anatomy imaged. This is referred to as the field of view.

### Number of excitations (NEX)

In collecting data to produce the final image the number of times each signal with the same slope of phase encoding is applied is called the number of excitations. The higher the NEX the more data collected.

### Signal to noise ratio

This is the ratio of the signal produced in the receiver coil to the average amplitude of the noise generated by the presence of the patient in the magnetic field. Noise occurs at all frequencies, is random in time, but constant for every patient, depending on patient build. The signal is cumulative and depends on many factors including the scan time. Scan time = TR x number of NEX. Scan time represents the time to completed image data acquisition and is important to maintain image quality, provided that it is not so long that patient movement occurs. Any movement by the patient reduces image quality.

Fig.6.2 T2 differences between fat and water

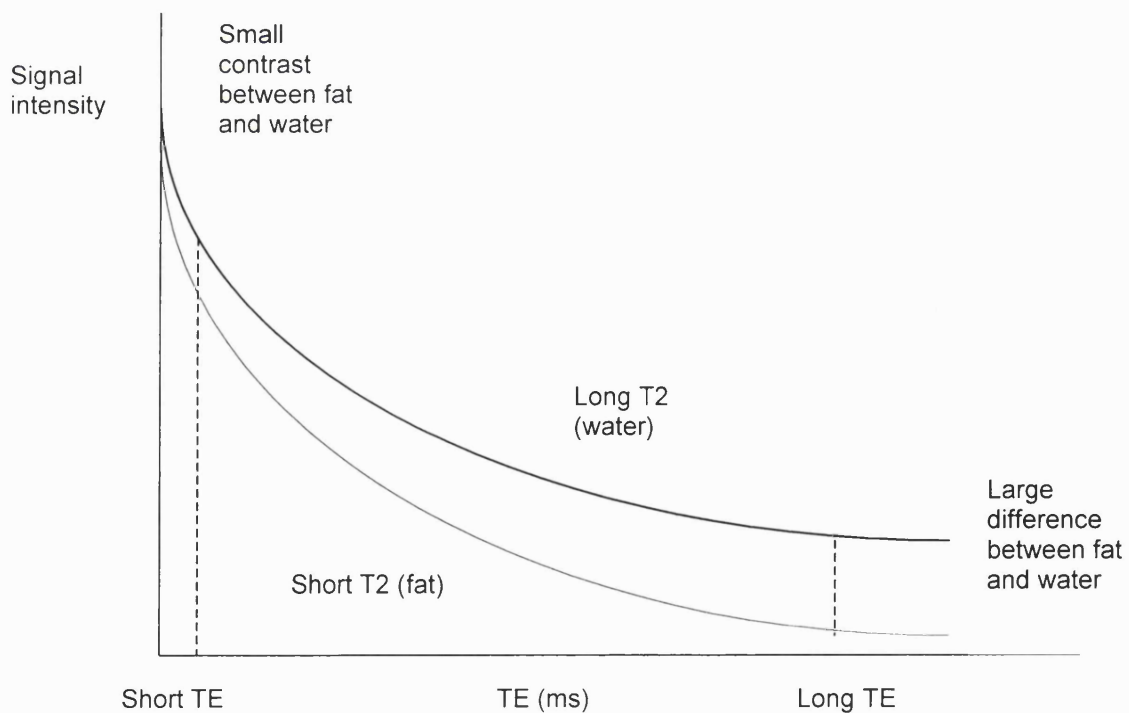
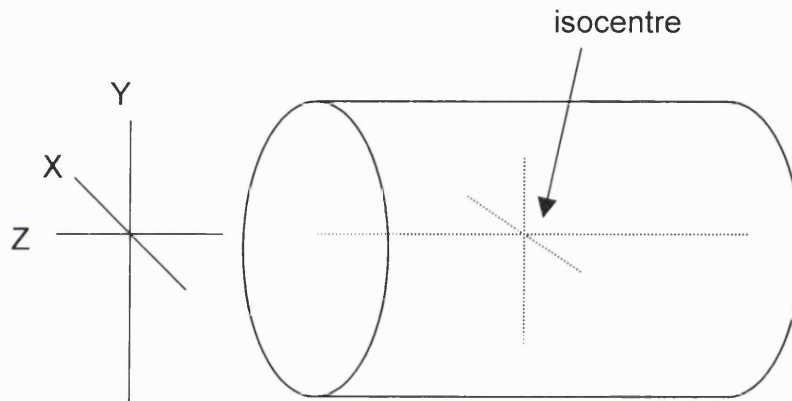


Fig 6.3. The X,Y and Z gradient axes



### MRI safety

Although no long term hazardous effects have been observed with MRI it is necessary to screen all personnel and patients before entering the scan facility.

This is done according to a screening form produced by The International Society for Magnetic Resonance Imaging (see appendix 1). Problems with image artefacts that occur due to subject movement can be reduced with proper attention to subject comfort and in keeping the scanning time as short as possible.

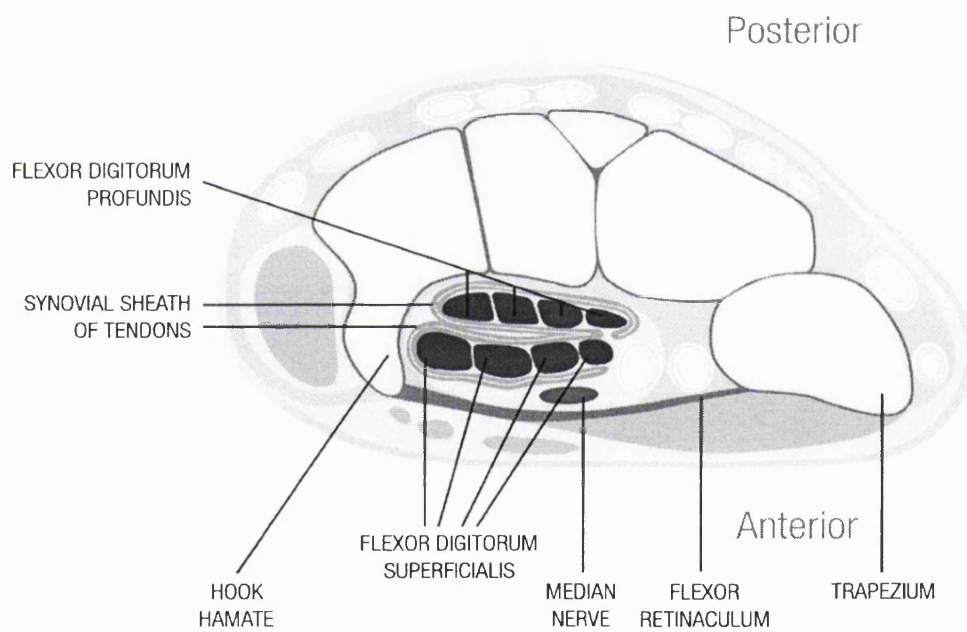
## 6.2 MRI and the anatomy of the carpal tunnel

High field (1.5T) MRI can display the contents of the carpal tunnel accurately allowing for the detection of both normal and pathological anatomy (Middleton et al 1987).

The anatomy of the carpal tunnel is shown in Fig.6.4. The carpal tunnel is a fibrous osseous tunnel through which the tendons of the finger flexors, the long thumb flexor and the median nerve pass. The posterior border is formed by the carpal bones, and the anterior border by the a thick ligamentous band, the flexor retinaculum. This ligament is attached to the hook of hamate and the pisiform bone medially, and radially is attached to the tubercle of the scaphoid and trapezium. It can be seen on MR images as an arching dark line above the superficial flexor tendons. More laterally the ligament is pierced by the tendon of flexor carpi radialis which runs in its own groove along the trapezium and remains technically separate from the carpal tunnel. The flexor muscles to the fingers originate from the common tendon on the medial epicondyle of the humerus, the anterior aspect of the radius, ulnar and interosseous membrane. The most superficial of the tendons within the carpal tunnel are the tendons of the flexor digitorum superficialis (FDS). These can be seen as four separate tendons passing through the carpal tunnel just beneath the flexor retinaculum to insert onto the middle phalanges. Deep to FDS lie the four tendons of the deep finger flexors the flexor digitorum profundus (FDP). This muscle arises from the proximal surface of the ulnar and inserts onto the four distal phalanges. The flexor pollicis longus tendon passes laterally on its way to insert onto the proximal phalanx of the thumb. All of the tendons in the carpal tunnel are surrounded by synovium forming the flexor synovial sheath, which allows for their smooth gliding motion. Generally an ulnar bursa separates the deep and superficial tendons and a separate bursa surrounds the flexor pollicis longus tendon.



Fig 6.4 Diagram of cross section through the carpal tunnel at the level of the hook of hamate



Movement of the flexor tendons anteriorly with wrist flexion has been observed (Zeiss et al 1989). The median nerve, which innervates all of the muscles mentioned above, sits superficially just beneath the flexor retinaculum, the superficial tendon to the index finger being usually the closest tendon to the nerve.

Using MRI with T2 weighted images the median nerve has a bright signal and is easily differentiated from the very dark flexor tendons.

### **6.3 Nerve movement with wrist flexion**

High field (1.5 T) MR systems and the use of surface coils have enabled high resolution images of nerves to be obtained (How et al. 1994). However while nerve movement with wrist flexion has been described qualitatively, nerve movement has not previously been measured quantitatively from MRI images. With wrist flexion an interposition of the nerve between the superficial flexor tendons has been reported in healthy subjects (Skie et al. 1990). A lack of interposition was observed in subjects with carpal tunnel syndrome (Allman et al. 1997). The tendency for the nerve to remain beneath the flexor retinaculum during wrist flexion means the nerve may become compressed during this movement.

## **6.4 MRI pilot study of median nerve movement with wrist flexion**

Our initial studies involved the use of a specialised MRI system (Niche scanner, Inner Vision MRI Ltd, London). This 0.17 T system allowed the subject to sit so that the arm could be abducted and placed inside the small magnetic tunnel.

In these pilot studies the overall aim was to assess the feasibility of using low field MRI to assess motion and shape of the median nerve relative to the finger flexor tendons at the carpal tunnel in six asymptomatic volunteers.

### **6.4.1 Methods**

Each subject was positioned with the arm abducted and positioned through a 12cm loop coil with the forearm taped to the coil support so that the wrist was free to flex. Using a 2.5 minute acquisition time T1/T2\* (see discussion ) weighted gradient echo sequences with TR/TE =60/15ms, FOV = 100mm, slice thickness 3mm, 256 x 256 matrix images were acquired with a NEX =10 to improve signal to noise ratio. Images were acquired in the wrist neutral, maximum flexion and maximum extension positions. Data was obtained in an axial orientation through the centre of the carpal tunnel.

### **6.4.2 Results**

It was possible to visualise the median nerve as an intermediate grey structure in between the black flexor tendons and the flexor retinaculum in all subjects. During wrist extension the nerve was observed to become flattened in the saggital plane between the

tendons and the retinaculum. Wrist flexion caused the flexor tendons to move anteriorly and the nerve to move in a transverse plane in a radial direction (see Fig. 6.5)

### **6.4.3 Discussion**

While we demonstrated that it is possible to visualise the median nerve using low magnetic field strengths it is clear from these scans (see Fig. 6.5), that the resolution with the 0.17T scanner is marginal. The T1/T2\* weighting used represents a TE and TR that is mid way between T1 and T2 parameters and one that after some imaging trials produced the greatest resolution of the median nerve. Subject arm position in 90 degrees of shoulder abduction and with full wrist extension was difficult to maintain with comfort and in many cases lead to arm movement.

### **6.4.4 Conclusion**

Median nerve motion relative to the flexor tendons is observed at the carpal tunnel during wrist flexion and extension when using low field MRI systems.

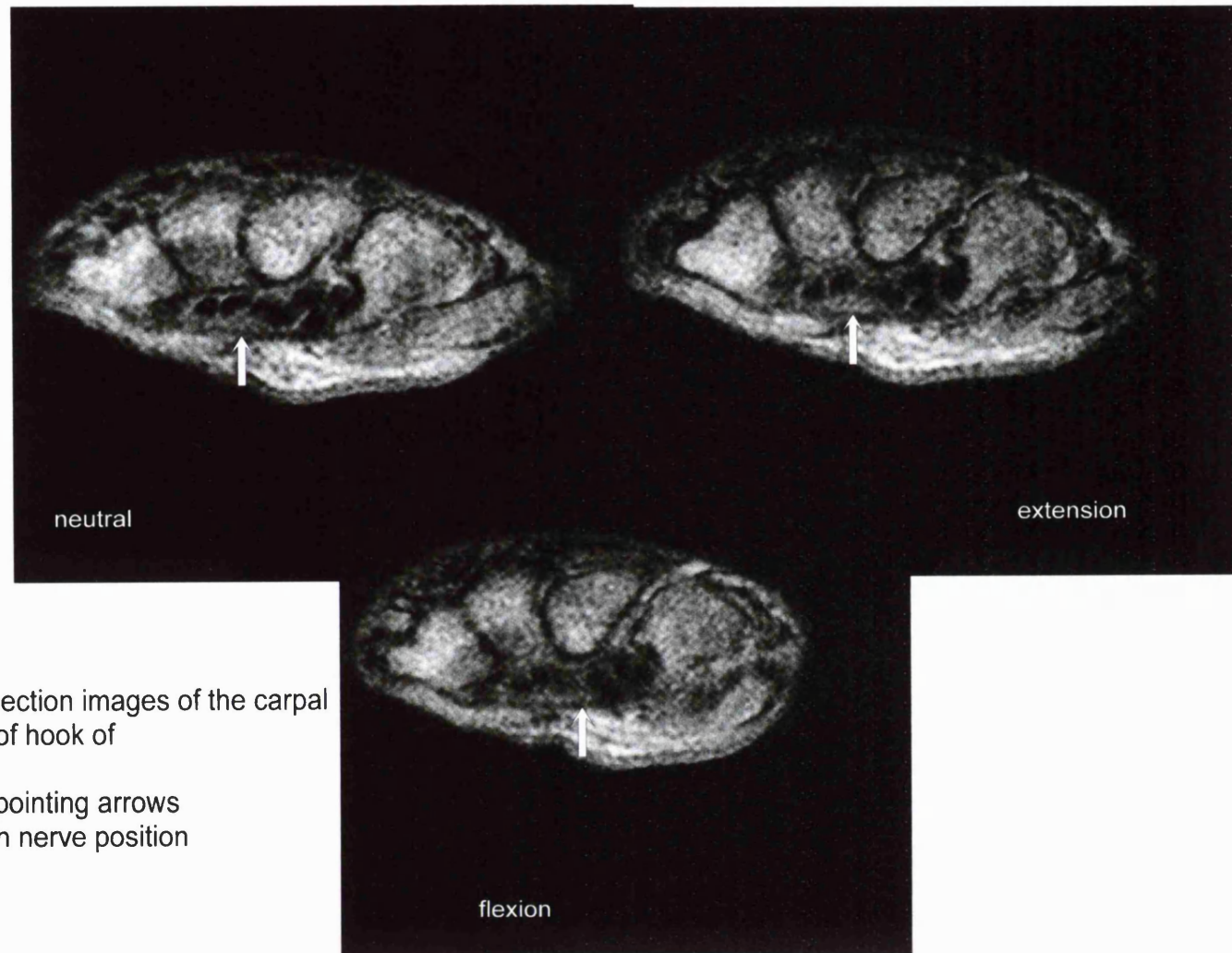


fig.6.5 Cross section images of the carpal tunnel at level of hook of hamate.  
White upward pointing arrows indicate median nerve position

### **6.4.5 Criticism of methodology**

While we showed it was possible to visualise the median nerve using a low field MRI system, this particular system did not allow the use of flow or fat suppression. The use of these parameters would be valuable in enhancing the contrast resolution of the images.

It became clear that the arm position required to obtain these images was:

- (i) Difficult to maintain with comfort which in some cases lead to subject movement and degradation of images
- (ii) Sustained shoulder abduction would be difficult for patients with NSAP to maintain
- (iii) Images with good resolution would be required for the quantitative analysis of nerve movement.

## **Chapter 7:**

### **Experiment 2: Magnetic Resonance Imaging and quantitative measurement of median nerve movement at the carpal tunnel in patients with non specific arm pain**

#### **7.1 Methods**

Seven patients were recruited from medical practices and physiotherapy clinics in London during December 1998 to February 1999. Three patients had been diagnosed with NSAP by Rheumatology Consultants, one by an Occupational Health Consultant and three by GPs. Prior to imaging, patients were examined to ensure they conformed to the subjective criteria for NSAP (Harrington JM 1998), and additionally to perform the upper limb tension test 1 (ULTT1) (Byng J. 1997, Slater H et al 1997). This test has been described in Chapter 5. Clinical findings from the upper limb tension test were graded. Grades were 0 = full range of movement without symptoms, 1 = moderate lack of elbow extension (90 – 150 degrees) with mild symptoms and 2 = severe lack of elbow extension < 90 degrees with marked symptom production. Patients with bilateral arm symptoms were asked to rate which side they thought was more severely affected. Table 7.1 summarises these results and other data on the patients.

Eight age and gender matched control subjects were recruited from among students and staff at University College London. The study was approved by University College London and University College Hospitals Ethical Committee and all subjects gave informed written consent.

We imaged 15 subjects, 7 patients (14 wrists) and 8 control subjects (15 wrists). Subjects were imaged lying supine in an open access MR scanner (OPEN Viva, 0.2T, Siemens Medical Systems, Erlangen, Germany). This has the advantage of increased subject comfort since they are not confined in a narrow tunnel system. Subjects were able to lie comfortably in a supine position so that the wrist could be imaged while the arm was by the side of the body with the elbow extended and the wrist immobilised in modified Futuro wrist splints. However the magnetic field strength is lower than closed scanners, which employ field strengths in the region of 1.5 to 2 T, and image resolution is consequently of a lower quality. Surface coils, which act as both RF transmitter and receiver of the MR signal were positioned around the wrist and splint to improve the signal to noise ratio. Foam padding was placed between the wrist splints and the coil to reduced "hot spot" effects on images caused by tissue coming to close to the coil. The padding also helped to support the wrist and reduce the risk of arm movement. When obtaining images for comparison it is obviously important that the same slices from the data acquisition are compared. Initial fast location scanning was performed in the sagittal plane to identify the RF coil centre position and to confirm the angle of the radio-carpal joint.

In our study slice acquisition started from the clearly seen radio –carpal joint space. The same number of slices at a constant slice thickness were acquired for each subject. Slice comparison at the level of the hook of hamate was chosen for our studies, since this is an easily visualised structure on the scans.

Of importance in object shape analysis is the angle at which the object is viewed. Factors such as these were considered when positioning the subjects within the scanner. The surface marking for the carpal tunnel is the distal wrist crease. This was observed prior to setting the wrist in the wrist splint and the splint marked accordingly and positioned within the centre of the surface coil.



The carpal tunnel was imaged in neutral, 30 degrees of wrist flexion and 30 degrees of wrist extension. Imaging the axial plane was performed on 8 contiguous 5mm slices aligned perpendicular to the nerve axis using a T2 weighted fast spin echo sequence (TE102, TR 1632, FOV 160x160mm, 256x256 image matrix, NEX 4) in a scan time of 4 minutes. Pixel size was consistent between all images at 0.63mm. The screening procedure and imaging of both wrists took approximately 1 ½ hours.

## **7.2 Results**

### **7.2.1 Clinical status of subjects**

We imaged 14 wrists from 7 female patients (average age 29 years, range 23-43 yrs). Patient occupations were secretary (4), journalist (1), computer operator (1) and graphic designer (1). The average duration of symptoms was 2.1 years with a range from 4 months – 7 years. Two patients were at present unable to work due to symptoms and four patients although at work had severely restricted their use of display screen equipment. One patient was markedly improved following physiotherapy treatment and had good hand function.

Nerve conduction studies were normal in the one patient tested. Symptoms of chronic aching over both the flexor and extensor aspects of the forearms were present in six patients and were associated with loss of hand function, particularly grip activities. Six patients complained of intermittent and diffuse paraesthesia over the palmar aspect of the hand and fingers. Where present this was reported to be more intense over the index and middle fingers. Clinical screening (see appendix 2) did not demonstrate specific upper limb or cervical spine pathology. In six subjects the upper limb tension test 1 demonstrated painful loss of elbow extension (see Table 7.1). Eight control subjects (15 wrists were imaged (average age 28.8 year, range 20-40 yrs). These subjects, who did

not report any history of neck or arm pain symptoms, were examined prior to imaging. All had full painfree movement of the cervical spine and upper limbs. All control subjects demonstrated full range of elbow extension when performing the upper limb tension test 1.

### 7.2.2 Analysis of nerve movement

Images of the carpal tunnel during wrist extension and flexion were analysed at the level of the hook of hamate and trapezium. Image slices were closely matched inter and intra subjects. The x-y co-ordinates were measured from landmarks as they appeared on the images. The landmarks chosen were the tip of the hook of hamate, centre of the median nerve and lowest medial border of trapezium and these were measured on each scan (see Fig 7.1). Measurements were made blind by two independent observers. Measurements within  $\pm 2$  pixels from two repeated measurements carried out by the independent observers were averaged. The 3% of points that differed by more than this were reviewed blind and the best estimate of the co-ordinates was agreed between the observers.

Table 7.1 Patient details with side and grading of upper limb tension test results

Patient	Age	Side of symptoms and severity	Upper limb tension test	Time since symptom onset
*indicates hand dominance				
1	43years	R=L*	L(2) R(1)	7yrs
2	27years	*R>L	L(2) R (1)	6months
3	28years	*L>R	L(2) R(1)	2years
4§	26 years	L>R*	L(0) R(0)	2years
5	23 years	*R>L	R(2) L(1)	2 years
6	27 years	*R>L	R(2) L(1)	1 year 2 months
7	32 years	*R=L	R(1) L(2)	4 months

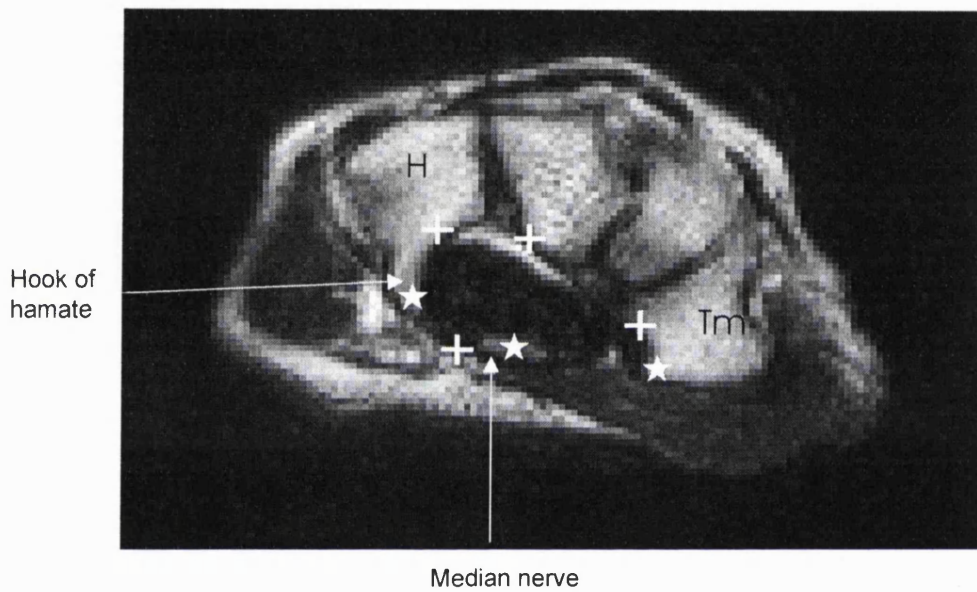


Fig 7.1 Cross section image of the carpal tunnel showing key landmarks for measuring ☆ nerve position and ⊕ cross sectional area  
**H=Hamate, TM=Trapezium**

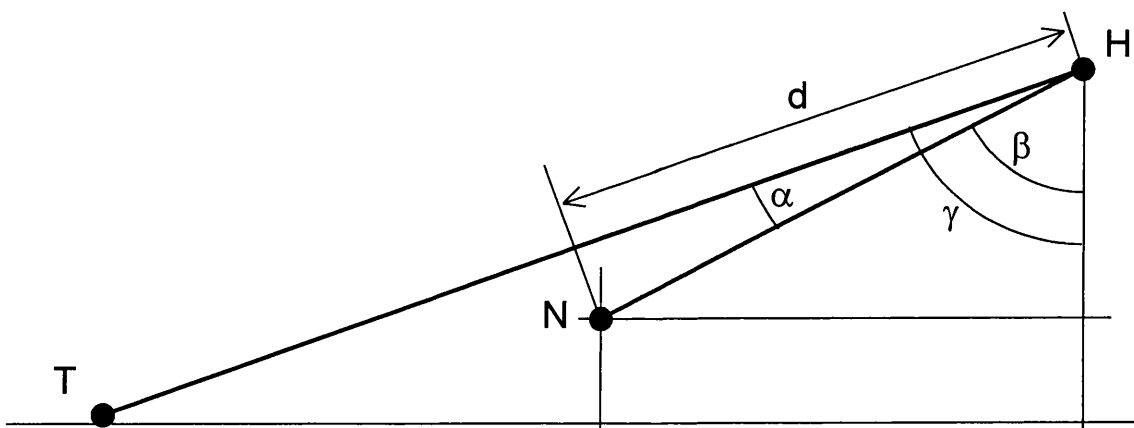
We calculated the distance,  $d$ , of the centre of the nerve (N) from the hook of hamate (H) in the direction from H to the medial edge of trapezium (T), using the co-ordinates of H, T, N. The spreadsheet calculated NH by pythagoras and the angle  $\alpha$  from the difference between  $\gamma$  and  $\beta$ , these latter 2 being calculated as arctan the ratio of the appropriate co-ordinate distances. Finally  $d (=NH \cos\alpha)$  was calculated. see Fig.7.2

The difference between this distance in flexion and extension was used as a simple measure of nerve mobility, since inspection of the images showed that this was the direction of nerve movement in control subjects. The intersection of this line by a perpendicular line from the centre of the median nerve (N) gave the distance the nerve travelled in a vertical plane i.e. an antero-posterior direction. Data from control subjects was compared with the most severely affected side in the patient group. One patient was much improved following physiotherapy treatment ( indicated by § in Table 7.1). Her results were analysed separately and were not included in the patient average.

### **7.2.3 Statistical analysis**

Data is presented as average  $\pm$  SE. Statistical comparisons were made using 2 tailed t-tests. Where both wrists were scanned, and for patients where both sides had marked symptoms, the average value for the two wrists was used. This method was employed as the most conservative means of analysing the data

Fig 7.2 Method for calculation of nerve(N) position in relation to Hamate (H) and Trapezium (T)



#### 7.2.4 Results from the upper limb tension test

Only the patient group reported symptoms and demonstrated a restricted range of elbow extension with this test. Patients with bilateral arm symptoms were asked to rate which side they thought was more severely affected.

Table 7.1 summarises these results and other data on the patients.

#### 7.2.5 Magnetic resonance images

Typical scans in flexion and extension from both a patient and a control subject are shown in Fig 7.3. During wrist extension the nerve was located anteriorly and is flattened in a sagittal plane, lying close to the flexor retinaculum (scans a and d, Fig 7.3). This location was close to its position in wrist neutral (data not shown). With wrist flexion the median nerve in the control subject moves in a transverse plane in a radial direction, and in addition moves in a posterior direction (scan b, Fig 7.3). In the patient (scan e, Fig 7.3) the nerve stays close to the flexor retinaculum and any radial movement is minimal.

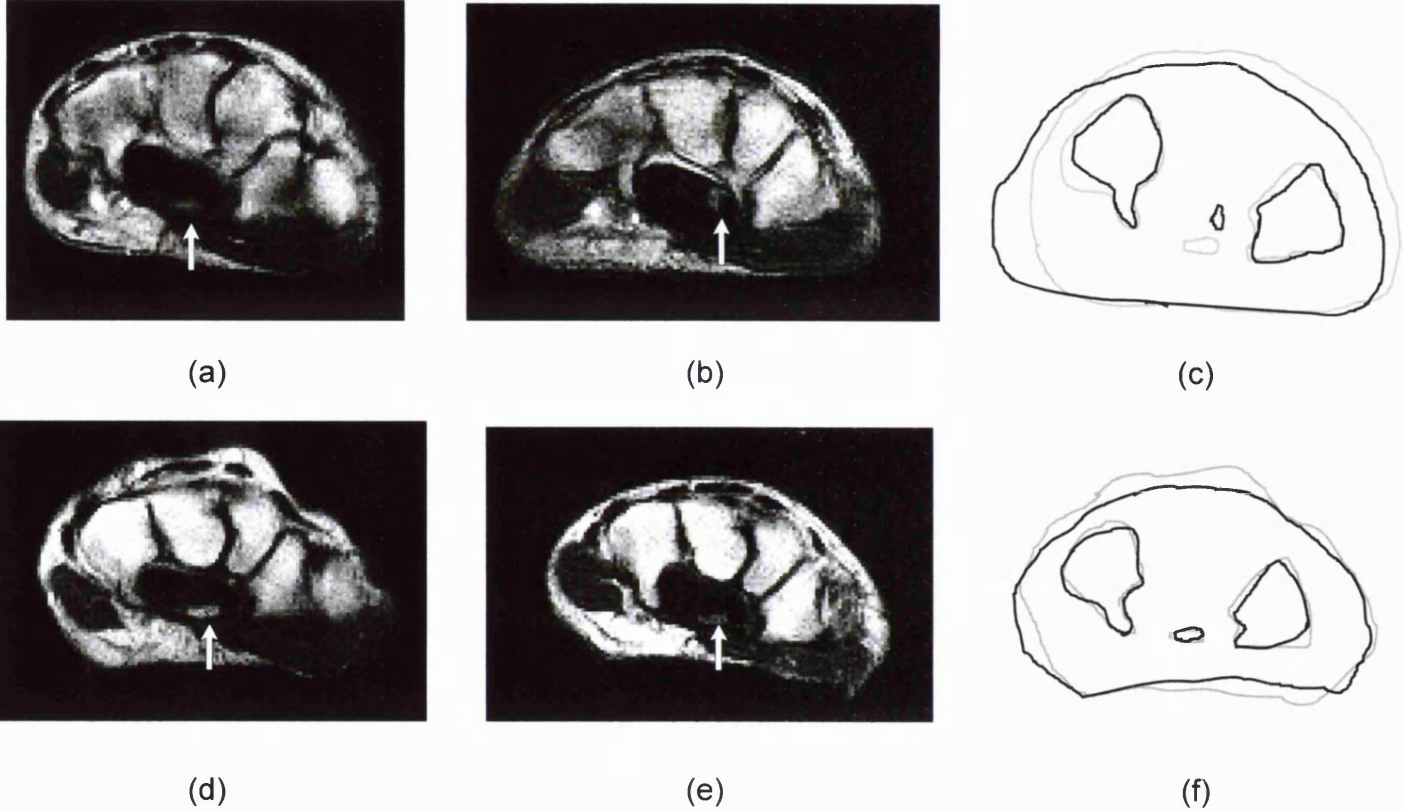


Fig 7.3

MR scans of the carpal tunnel during wrist extension (a) and flexion (b) in a control subject and (d) wrist extension and (e) flexion in a patient. Image overlay (c) and (f) are drawn from scans of the control subject and patient. Overlays show the position of the median nerve during extension (grey line) and flexion (black line). Small white arrow indicates median nerve

102.

### 7.2.6 Nerve position in relation to wrist position

In most subjects, both patients and controls, the nerve was roughly mid – way across the carpal tunnel in extension, the average hamate to nerve distance, (measure D) being  $11.94 \text{ mm} \pm 0.58 \text{ mm}$  for controls (n=8) and  $10.52 \text{ mm} \pm 0.55 \text{ mm}$  for the patient group (n=6). However in flexion the nerve position was quite different. In controls the nerve was found to be further from the hamate at  $15.14 \text{ mm} \pm 0.49$ . In contrast in patients the nerve was at  $11.54 \text{ mm} \pm 1.03 \text{ mm}$ . The difference in flexion is very significant (2 tailed t-test) ( $p=0.015$ ) See Fig. 7.4

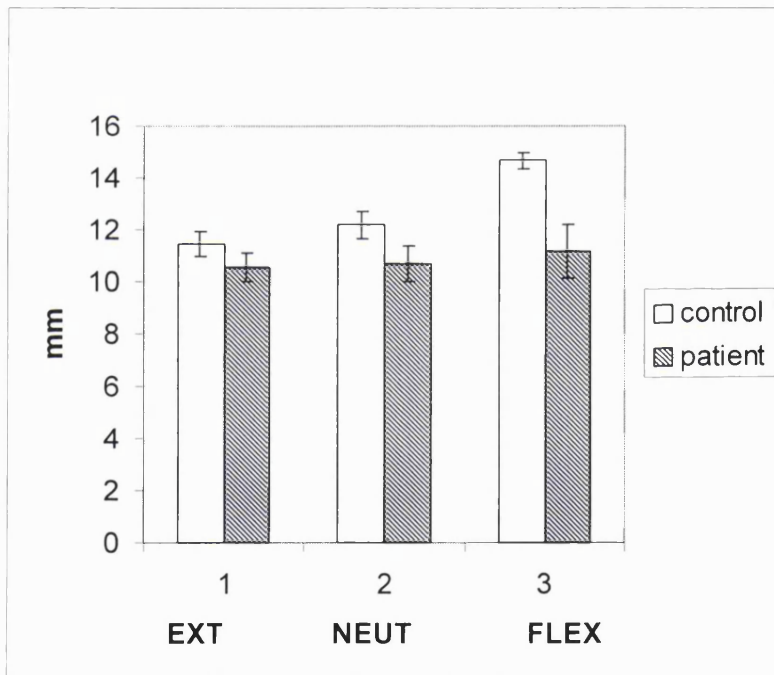


Fig 7.4 Average values for the position of the median nerve relative to the hamate in the hamate-trapezium plane during extension, neutral and wrist flexion positions



### **7.2.7 Analysis of nerve movement between wrist extension and flexion**

Overall from extension to flexion the control group had a mean horizontal translation in a radial direction of  $3.24 \text{ mm} \pm 0.50\text{mm}$ , and a range of 1.2 – 5.4mm. For the patient group the mean was  $1.02\text{mm} \pm 0.64\text{mm}$  with a range of -1.09, to 2.2mm (– sign indicates movement in a ulnar direction), (  $p= 0.015$ ) (See Fig 7.5).

When the distribution frequency for nerve translation was compared between the two groups, two distinct populations emerged (See Fig 7.6).

### **7.2.8 Analysis of nerve movement in an antero-posterior direction**

Mean movement in an antero posterior direction was  $1.62 \text{ mm} \pm 0.47 \text{ mm}$  in controls and  $1.42 \text{ mm} \pm 0.40 \text{ mm}$  in patients, a difference that was not significant ( $p = 0.76$ ).

### **7.2.9 Individual trends within the patient group**

Three patients experienced severe unilateral symptoms. In two the median nerve showed much less movement on the severely affected side compared to the less affected side ( $-0.8 \text{ mm} / 4.9\text{mm}$  and  $-2.9\text{mm} / 3.9\text{mm}$ ). In the third patient there was a marked ulnar movement of 5.3mm on the non symptomatic side. In the one patient who had recovered following treatment the nerve moved 2.8mm radially, close to the control average.

Fig 7.5 Lateral translation of the median nerve, averages for both wrists

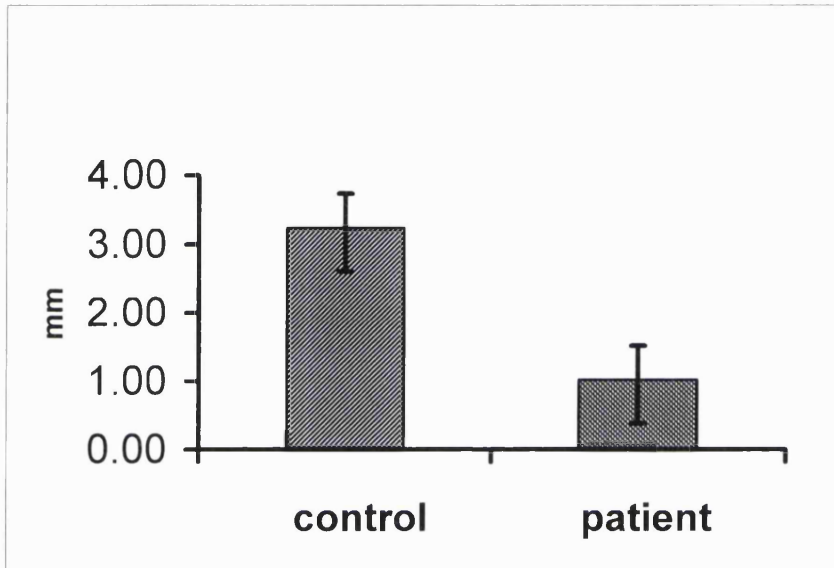
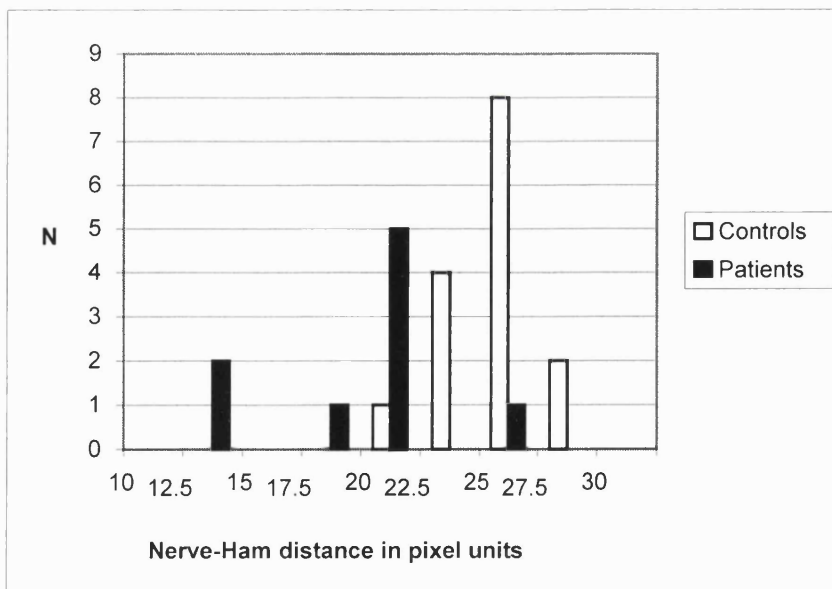


Fig 7.6 frequency histogram Nerve- Hamate distance with wrist flexion



### 7.2.10 Analysis of carpal tunnel area

Measurements were made by a single observer of the co ordinates of the extreme lateral, medial, anterior (flexor retinaculum) and posterior bony edges of the carpal tunnel (see Fig 7.1). From the co ordinates of the extreme medial and lateral edges of the carpal tunnel, the maximum width (w) was calculated. Similarly the maximum depth (d) was calculated for the more anterior and posterior co ordinates. Area was estimated as  $\pi.w.d/4$ , i.e. assuming the tunnel was an ellipse. Dimensions and area were again compared between the controls and the most symptomatic side in the patients.

The mean area of the carpal tunnel in the control group was  $2.33 \text{ cm}^2 \pm 0.07 \text{ cm}^2$  range 2.62 – 1.73  $\text{cm}^2$ . For the patients the mean was  $2.05 \text{ cm}^2 \pm 0.08 \text{ cm}^2$ , range 2.38 – 1.8  $\text{cm}^2$  a significant difference ( $p = 0.02$ ).

The change in area was due mostly to a difference in tunnel width (medial to lateral), the control average width being  $24.98 \pm 0.17 \text{ mm}$  whilst the patient average was  $23.01 \pm 0.11 \text{ mm}$  ( $p = 0.0005$ ). The depth (antero posterior) showed a smaller difference being  $11.88 \pm 0.31 \text{ mm}$  in controls and  $11.39 \pm 0.50 \text{ mm}$  in patients ( $p = 0.24$ ).

Nerve movement from wrist extension to wrist flexion, normalised for carpal tunnel width remained significantly different  $p=0.007$ .

Distance Hamate, Nerve (ext-flx)/distance Hamate, Trapezium

Control average	14.2%
S.E.	1.7%
Patient average	4.1%
S.E.	3.4%
Two tailed "T" test equal variance C v's P	0.007

### 7.3 Discussion

Radial movement of the median nerve with wrist flexion has previously been described in controls by MRI and Ultrasonography (Nakamichi and Tachibana 1995, How et al. 1994). This small group of typical NSAP patients show only 31% of the normal radial translation on flexion. This is similar to CTS patients, as described qualitatively on MRI (Allman et al. 1997). Therefore although NSAP patients do not show conduction velocity changes or muscle atrophy, as in CTS, they appear to have reduced nerve mobility. This fits with the information from the ULTT1 test that is designed to test nerve movement in the arm.

There is a significant trend for this highly selected group of NSAP patients to have a smaller cross section area of the carpal . The literature on the size of the carpal tunnel as a risk factor for carpal tunnel syndrome is however inconclusive (Francis and Habes 1990, Bleeker et al. 1985) A much larger group of subjects are needed to assess the true significance of this anthropometric detail.

Compared to previous studies, nerve movement in this study was observed at relatively small angles of wrist movement (30 degrees compared to 40 and 45 degrees) (Allman et al 1997, How et al 1994). In addition images were obtained with the subject supine and with the shoulder slightly abducted (by 10-15 degrees) and elbow extended. The common position employed to image the carpal tunnel with high field scanning requires the subject to be prone with the arm elevated. Shoulder abduction may change the position of the median nerve at the carpal tunnel, increase tension within neural tissue and subsequently bias nerve mobility (Wright 1996).

More work is needed to confirm and extend the patient results presented here. But we conclude that NSAP patients may be distinguished, on their affected or more severely affected

side by the relative position of the median nerve in wrist flexion. These images were obtained using a relatively low field scanner. Scanners with similar field strength are available in many hospitals and are less expensive to use than high field scanners .

#### **7.4 Criticism of methodology**

1. MRI using the protocols employed here is time consuming and an inherently expensive tool for the investigation of nerve movement.
2. Real time investigation of nerve movement is not possible.
3. We were unable to investigate nerve signal strength as an indication of neural oedema since high field magnetic resonance imaging is required for this.
4. High field imaging using gadolinium enhancement would allow visualisation of nerve blood perfusion giving an indication of hyperaemia caused as a result of nerve trauma (Sugimoto 1994).

Ultrasound imaging is a cheaper alternative to MRI since clear images of the median nerve can be obtained using high frequency systems (Gibbon 1996) and this methodology has proved useful for imaging the median nerve in patients with carpal tunnel syndrome (Duncan et al. 1999, Buchberger 1997).

The results from this paper have been published: Greening J, Smart S, Leary R, Hall-Craggs M, O'Higgins P, Lynn B. Reduced movement of the median nerve in carpal tunnel during wrist flexion in patients with non-specific arm pain. *Lancet* 1999;354:217-8

## Chapter 8: Ultra sound imaging

### 8.1 Basic ultrasound imaging

Ultrasound (u/s) is defined as sound with a frequency above the upper limit of human hearing. This value is 20 kHz, however frequencies used for medical diagnostic imaging are much higher, in the range from 3.5MHz – 20MHz. In practice ultrasound is transmitted to the patient in short pulsed bursts (1/10000 of a second). Echoes returning from different tissue are compiled to form images.

Ultrasound waves are produced by the reverse piezo electric properties of lead zirconate titanate (PZT). The shape change in PZT produced when exposed to an electrical potential generates the ultrasound wave. Pulses are transmitted along a narrow beam which is swept over the area to be imaged and echoes from a thin slice of tissue are collected. In this respect ultrasound imaging is similar to MRI, however ultrasound does not produce a full cross section image of the patient and the ultrasound can be orientated within any plane of the three dimensional volume imaged. The usefulness of ultrasound as an imaging tool is the result of reflection and scattering at different organ and tissue boundaries within the subject.

Ultrasound travels through tissues at a speed of 1540metres / second,  $\pm 3\%$ .

Different tissue allows u/s to pass at different speeds depending on their own acoustic impedance. Acoustic impedance of a tissue is the measure of its efficiency in allowing the passage of u/s waves. It is proportional to a tissue's density and compressibility. It is very low for air, medium in soft tissue and high for bone. The echoes required to produce images are generated from the junctions between tissue of different acoustic impedance. A soft tissue/air interface or a soft tissue / bone interface will produce a very large acoustic difference, giving rise to an almost 100% reflection of ultra sound waves.

The majority of interfaces in patients are small, irregular in shape and produce a scattering of the ultrasound beam. Large numbers of echoes are produced, a minority of which return to the ultrasound transducer and permit detection of the interface. This reflection is referred to as scattering.

In addition to scattering at a tissue interface the direction in which the sound beam is travelling may be refracted if it hits the interface surface at an angle. Refraction of the sound beam may result in the mis-placement information in ultrasound images. It is therefore essential that the ultra sound beam be kept at 90 degrees to the structure to be imaged, but note that with non-planner structures, i.e. most structures in the body this is unlikely.

### Absorption

Ultra sound energy is lost through numerous processes associated with the imperfect transfer of mechanical energy from the sound pulses to the tissues. The absorbed energy appears in the tissues as heat. Absorption is approximately proportional to the ultrasound frequency and limits deep imaging with high (10-20MHz) transducers.

### Attenuation

The progressive reduction in the strength of the ultrasound pulses and therefore echoes, is the sum of all the energy lost from the pulse, mostly through absorption and refraction.

The overall effect is to cause a major reduction in the strength of the echoes returning from the deep tissues.

## Phased array Transducers

These are linear transducers 2-3 cm in length with 40-128 strips of piezo-electric material. Each element of the transducer is controlled individually and is fired in a rapid sequence. The resulting individual sound waves from each element combine to form a wave front, which travels at right angles to itself. The degree of delay between firing of the individual elements can be varied, enabling the angle at which the wave front travels to be varied.

Signals returning to the transducer can be delayed by time increments identical to those between energizing the individual elements in transmission mode so that the returning signals can be summated to compile each line of the image.

This transducer also allows the beam to be focused. The distance to the focal point of the beam being determined by the degree of curvature of the wave front. The major advantage of focusing is that it allows the beam width to be varied so that the narrowest portion is used at the depth of importance for the individual tissue to be imaged.

## Resolution

Axial resolution is the ability of the ultrasound system to discriminate between two closely aligned structures lying along the length of the ultra sound beam. Axial resolution is proportional to the ultrasound wavelength and the theoretical minimum value is half the wavelength. As ultrasound frequency increases the wavelength decreases and there is a proportional increase in resolution. Wavelength is proportional to speed of propagation of the ultrasound, approximately 1540m/s or 1.54mm/ $\mu$ s divided by frequency.

Wavelength (mm)=1.54mm/ $\mu$ s / frequency (MHz).



Therefore for a high frequency system of 15 MHz the approximate axial resolution would be 0.1mm, at 20 MHz this would be 0.07mm. However it is important to remember that at higher frequencies depth penetration is less. At 15-22 MHz depth penetration would be reduced to approximately 2cm. However this depth is very suitable for imaging superficial structures such as the superficial tendons and some nerves.

### Lateral resolution

This represents the ability of an ultrasound system to discriminate between two closely adjacent structures at the same depth from the transducer surface. It is determined by the beam width at that particular depth. If the lateral separation between two reflective surfaces is greater than the beam width then two separate echoes can be produced which will be resolved as two separate reflectors. Focusing the beam width is therefore important in increasing lateral resolution.

## **8.2 Imaging peripheral nerves with high frequency ultrasound**

The high resolution obtained with high frequency (15-20MHz) ultrasound makes possible the identification of peripheral nerves including their internal fascicular arrangement. Peripheral nerves have a typical ultrasound structure that correlates well with their histological appearance (Silvestri et al. 1995), making differentiation between nerve and tendons and other adjacent structures possible. Peripheral nerves are described as having a typical arrangement of their internal structure. On longitudinal images they appear to have multiple but discontinuous hypoechoic bundles separated by hyperechogenic tissue ( Martinoli and Derchi 1999). (See Fig 8.1). On axial scans nerves have multiple rounded hypoechoic areas surrounded by a hyperechogenic background (see Fig 8.2). These hypoechoic areas appear to correspond to fascicular structures surrounded by neural connective tissue. This

appearance may be caused by the different ultrasonic scattering properties of the relatively homogeneous neuronal tissue versus the adipose and small vessel content of connective tissue, which is hyperechoic. However the fascicular structures seen on ultrasound may not entirely represent those present on histological assay (Silvestri et al. 1995). One explanation maybe that due to the undulating course of peripheral nerve trunks some fascicles may remain oblique to the ultrasound beam and remain undetected.

At these high ultrasound frequencies depth penetration of tissue is less (approximately 2cm), restricting evaluation to the more superficial peripheral nerves such as the median and ulnar nerves in the forearm and wrist. Transducers in the 10MHz range still allow the visualisation of peripheral nerves, but at less resolution. However tissue penetration is greater allowing visualisation of deeper structures such as the sciatic nerve in the thigh.

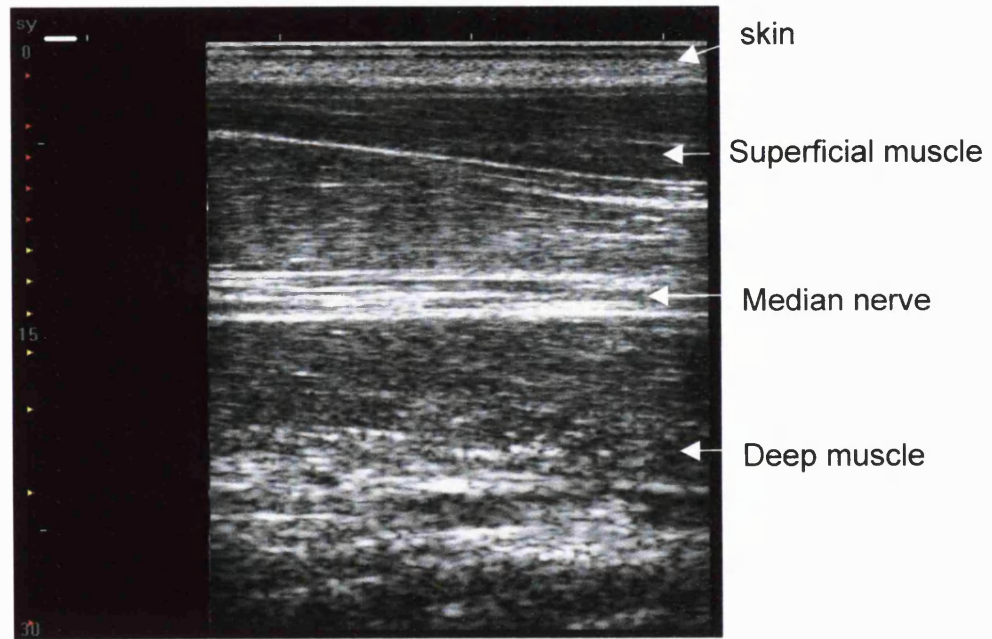


Fig. 8.1 High frequency (10-22 MHz) ultrasound image of longitudinal section through distal forearm showing the median nerve with a typical hyperechoic and hypoechoic appearance. Markers on left side of image are 1mm apart. Markers at the top of the image are 10mm apart

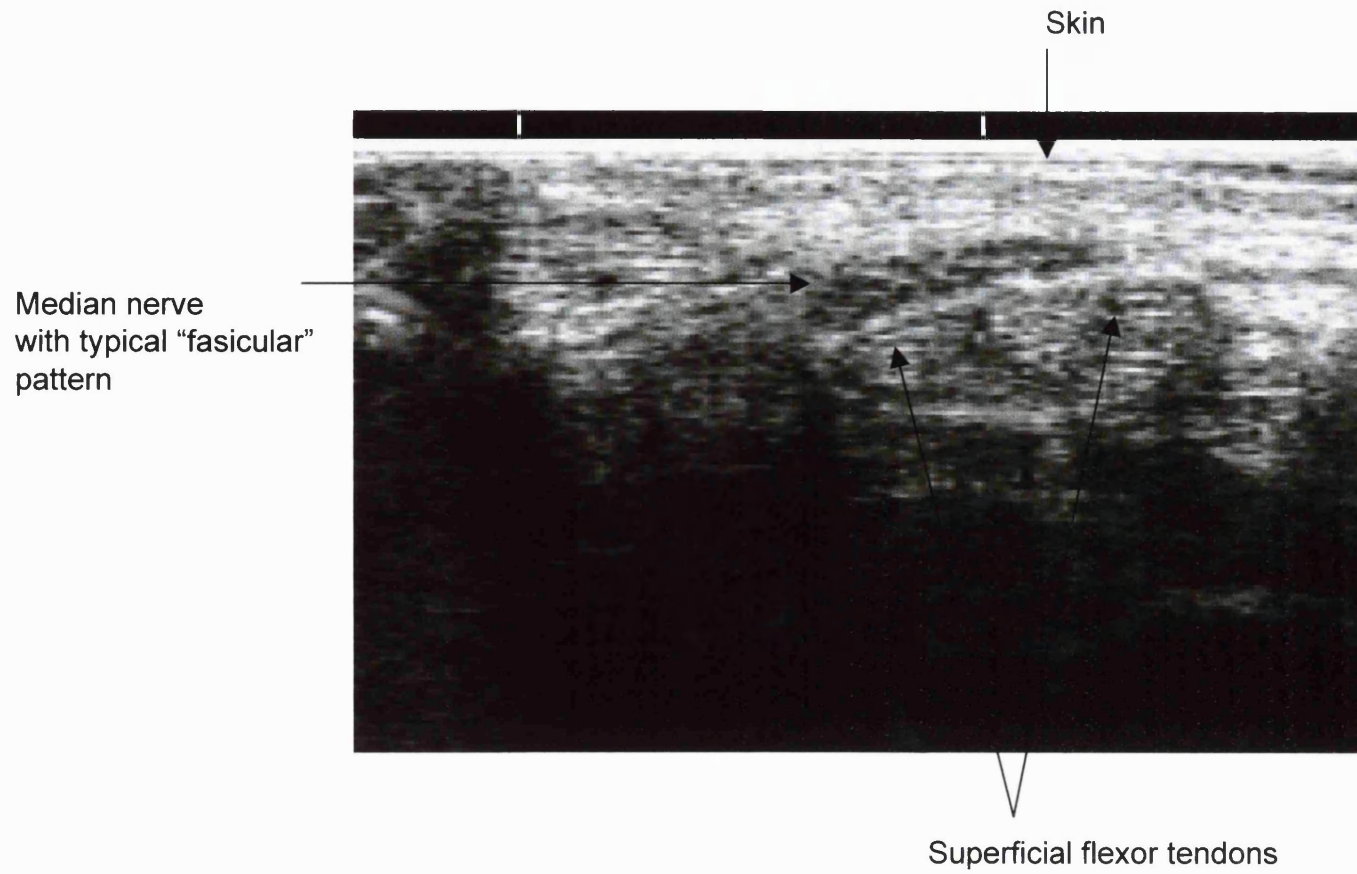


Fig.8.2 High frequency (10-22 MHz) cross section ultrasound image of the median nerve at the proximal carpal tunnel

## **Chapter 9:**

### **Experiment 3: The use of ultrasound imaging to demonstrate reduced movement of the median nerve during wrist flexion in patients with non-specific arm pain**

#### **9.1 Methods**

The patients (n=14) were referred from specialist clinics and were clinically screened prior to imaging, using the criteria set out by Harrington et al (1998) (see chapter 7). Of the 14 patients referred, 12 met the diagnostic criteria. Of the two patients excluded from the study, one had tenosynovitis and the second had recovered following physiotherapy treatment.

As part of the screening examination, the upper limb tension test (ULTT1) (Butler1991) was performed. In this study the ULTT1 test was assigned a score as described in methods section of Chapter 7.

Of the 12 patients included in the study, 1 was male and 11 were female and their ages ranged from 26-39 years (mean 33yr)( see Table 9.1). Body weight and height were recorded for 11 of the twelve patients. Mean body weight averaged 67Kg  $\pm$ 10,SD and height averaged 1.68m  $\pm$ 0.08,SD. The median nerve was imaged in both wrists for ten patients and in only the right wrist for two patients.

The 16 control subjects (13 female, 3 male) included colleagues and ex-colleagues who were of similar age to the patients (range 17-48, mean 30 years). Body weight and height were recorded for 15 of the 16 control subjects and mean weight was 65 Kg  $\pm$ 12,SD and height 1.67m $\pm$ 0.10, SD, close to the values for the patients

<i>Patient</i>	<i>Gender</i>	<i>Age</i>	<i>Side of symptoms and severity</i>	<i>Results ULTT1</i>
1	F	33	R	R(1)
2	F	34	L=R	L(1),R(1)
3	F	39	L>R	L(2),R(1)
4	F	26	L=R	L(1),R(1)
5	F	32	L=R	L(1),R(1)
6	F	32	R	R(2)
7	M	36	L=R	L(2),R(2)
8	F	32	R>L	L(0),R(2)
9	F	27	L	L(2),R(0)
10	F	37	L.R	L(1),R(0)
11	F	32	L.>R	L(2),R(1)
12	F	39	R>L	L(1),R(2)

Table 9.1. Data for patients with non-specific arm pain

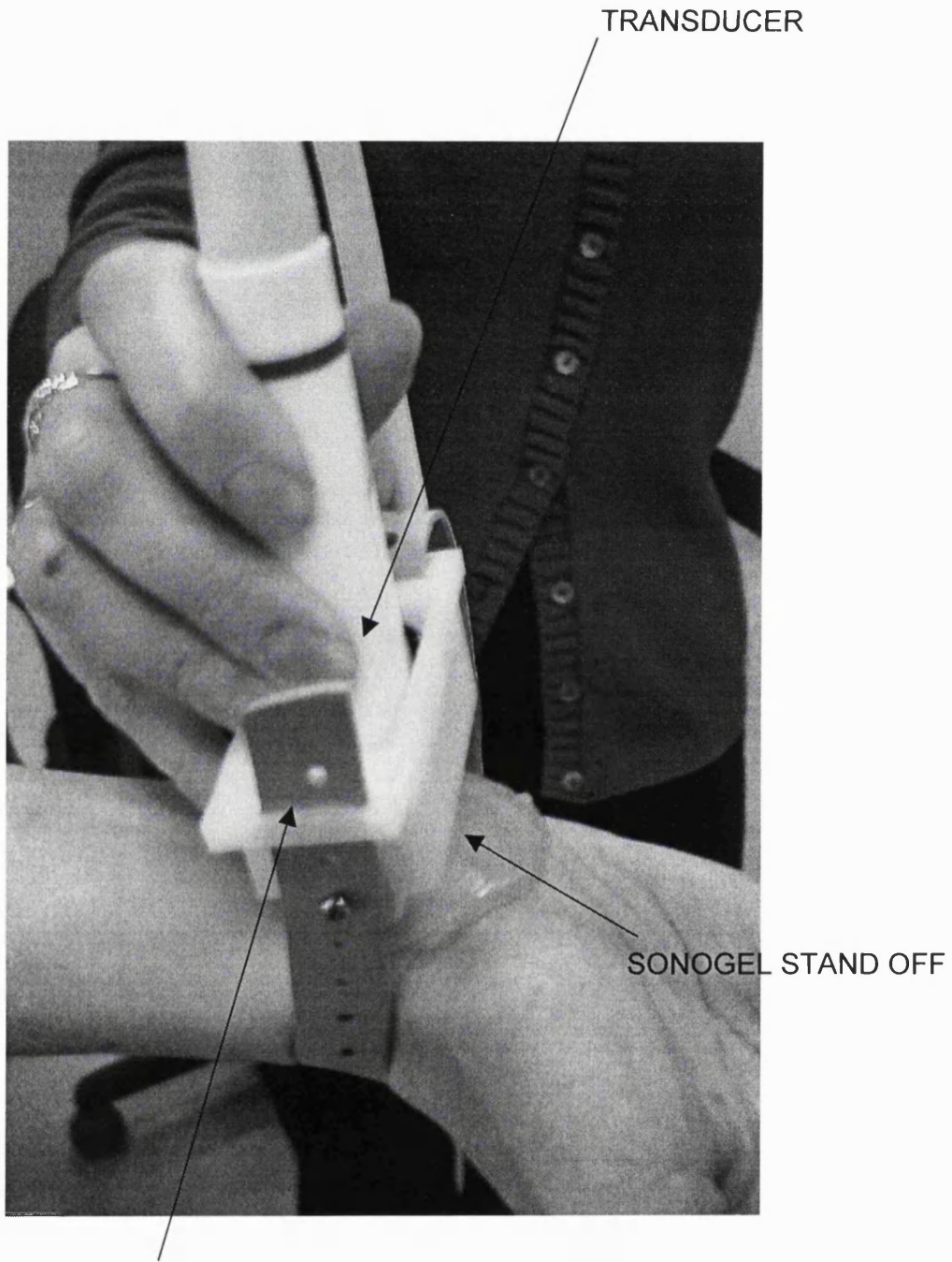
All were given a physical examination to exclude upper limb and cervical spine problems and to perform the ULTT1. The median nerve was imaged in both wrists in 9 control

subjects, but in only one wrist in the remaining 7 (6 right, 1 left). The study design was approved by the local ethical committee.

Imaging was performed using a linear array ultrasound probe (width 26 mm) running at 10-22 MHz (Dynamic Imaging, Diasus). Subjects lay on an examination couch with their arm at the side with the elbow fully extended and the shoulder abducted for comfort by 10-20°. The forearm was pronated and the transducer held against the ventral surface of the wrist at the level of the distal crease line. This posture was the same as used previously for the MRI study. In 11 controls and 9 patients the scanning head was lightly strapped in place using a special holder. This holder located the scanning head at right angles to the skin and was held in place by an elastic strap adjusted to just keep the scanning head securely in place but without exerting excessive pressure on the wrist (see Fig 9.1). In these subjects the transducer was separated from the skin by a 6 mm thick "stand-off" layer of Sonogel (Vertriebs GmbH). In remaining subjects the scanning head was held in contact with the skin by the operator.

Images were taken with the wrist in 30° extension, neutral and 30° flexion. The wrist was held in position using light plastic splints that ran along the back of the hand and on to the lower forearm. Three splints were used, one straight and two with 30° angles. The forearm and hand were lightly taped to the splints so that the proximal and distal interphalangeal joints were held at 0 degrees (see Fig 9.2). Small adjustments were made to the angle of the transducer to maintain the ultrasound beam orthogonal to the plane of the median nerve. These adjustments were <10° and the transducer was kept on the distal crease line for all 3 positions of the wrist. The results of the ULTT1 test were not known to the staff carrying out the imaging.

Fig 9.1 Position of ultra sound transducer at proximal wrist crease





The surface of the skin was marked using thin (approximately 2 mm wide) strips of tape (Fixamole, Belersdorf) fixed along the long axis of the palmar surface of the wrist (See Fig 9.3). Two strips were positioned 10-17 mm apart and could be seen on images as bright lines at the skin surface that cast an acoustic shadow across the image. Nerve location was measured relative to the surface markers (see Fig 9.4). Co-ordinates of the markers and of the centre of the nerve were measured off-line on bitmap images using the tpsDig program (F. James Rohlf, Department of Ecology and Evolution, State University of New York). The distance of the centre of the nerve from the markers in the horizontal and vertical directions was determined from the appropriate co-ordinates. Where 2 markers were visible, nerve distance from the midway point between the markers was used. Change in nerve position was measured by subtracting the values in flexion from those in extension.

Co-ordinates were defined such that positive values for horizontal movements indicate movement in the radial direction while positive values for the vertical measures indicate posterior movements (i.e. towards greater depth). Nerve area was measured from scans while the wrist was in the neutral position. This was done by marking the widest points on the nerve outline and then two points on the upper and lower edges approximately orthogonal to a line between the first two points and at a place of maximum nerve depth. Nerve area was calculated from these values assuming the nerve was ellipsoid. This data also allowed the nerve aspect ratio (ratio of the width to depth) to be calculated.

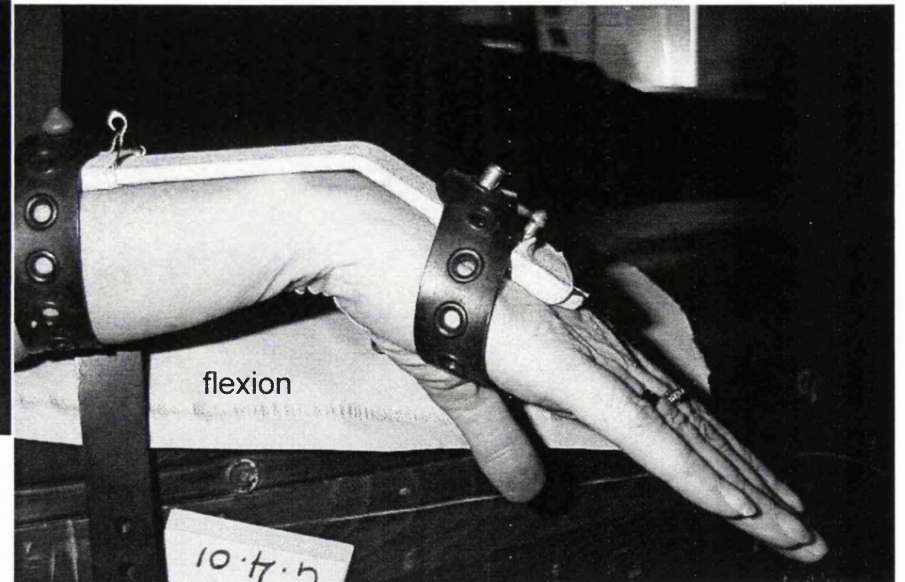
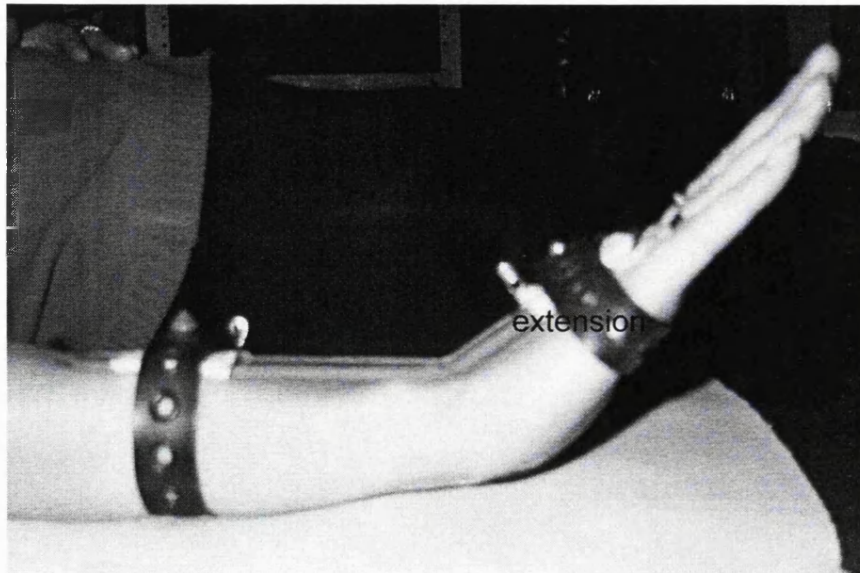


Fig 9.2 Wrist held in 30 degrees of extension and 30 degrees of flexion by wrist splints

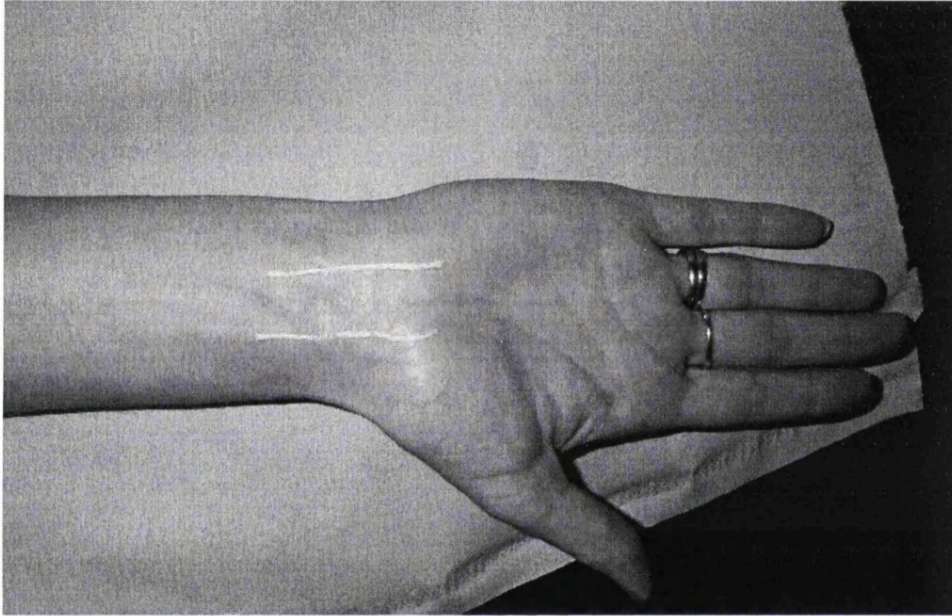


Fig 9.3 Fixamole tape position at the wrist

## 9.2 Statistical Analysis

Comparisons between movements in patients and controls were carried out using t-tests and error values are for standard errors, unless otherwise stated. Where both wrists were measured and where either both were symptomatic or both non-symptomatic average values for each subject have been used in comparisons between patients and controls. For the three patients where only one wrist was symptomatic, the value for the affected side was used. Where repeat measurements were made on 2 occasions (1 subject) the average value was used for comparisons. In looking at the correlation between nerve movement and the results of the ULTT1, and for the frequency distribution chart in Fig 9.7, we have used data from all wrists. In this case a total of 19 symptomatic wrists and 25 control wrists have been included. Analysis of variance (Newman-Keuls multiple comparison test) has been used for the comparison of means between patients scoring 1 and 2 on ULTT1. All image files were anonymously labelled and measured blind.

Co-ordinates were defined such that positive values for horizontal movements indicate movement in the radial direction while positive values for the vertical measures indicate posterior movements (i.e. towards greater depth). Nerve area was measured from scans while the wrist was in the neutral position. This was done by marking the widest points on the nerve outline, and then two points on the upper and lower edges approximately orthogonal to a line between the first two points and at a place of maximum nerve depth. Nerve area was calculated from these values assuming the nerve was ellipsoid. This data also allowed the nerve aspect ratio (ratio of the width to depth) to be calculated.

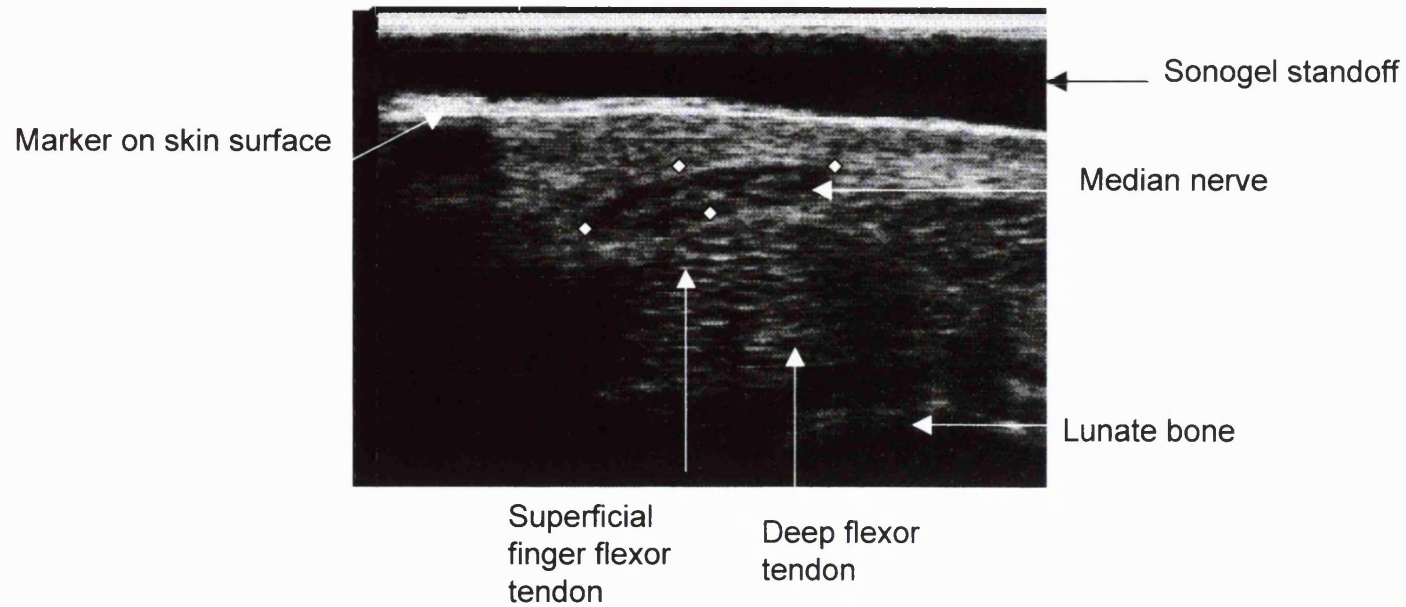


Fig 9.4. Axial view through proximal carpal tunnel to show position of nerve, superficial and deep flexor tendons. Wrist in neutral position, fingers at 0 degrees. Image obtained while using a 6mm sonogel "standoff".

◇ = coordinates used for nerve shape analysis and for the calculation of the centre of the nerve

## 9.3 Results

### 9.3.1 Control subjects

All control subjects were without sign of musculoskeletal dysfunction, had full range of elbow extension and no symptoms on testing the ULTT1 (i.e. scored 0). In this group there was a mean translation of the median nerve, in a radial direction, of  $4.78 \pm 0.42$  mm in  $30^\circ$  wrist flexion compared with the location in  $30^\circ$  extension (Fig 9.5). The change in lateral position between extension and flexion varied from 1.2 to 7.9 mm for all 25 wrists in the 16 control subjects (Fig 9.7). The nerve position was always more radial on flexion. On average, left and right wrists (measured in 9 control subjects) were similar. The variability between left and right sides in the same subject (mean square from analysis of variance,  $2.5 \text{ mm}^2$ , degrees of freedom = 8) was not significantly smaller than the variability between subjects (mean square  $3.9 \text{ mm}^2$ , d.f. 8). The median nerve also moves to a deeper location relative to the skin on the palmar surface of the wrist on moving from  $30^\circ$  extension to  $30^\circ$  flexion. The centre of the median nerve was only  $2.44 \pm 0.10$  mm from the surface in extension but was  $4.50 \pm 0.13$  mm from the surface in flexion, an average change of  $2.06 \pm 0.03$  mm. For all wrists the average nerve area in the wrist neutral position was  $6.97 \pm 0.51 \text{ mm}^2$  (range 4.01-12.2), and average aspect ratio was  $2.54 \pm 0.15$  (range 1.87-4.9).

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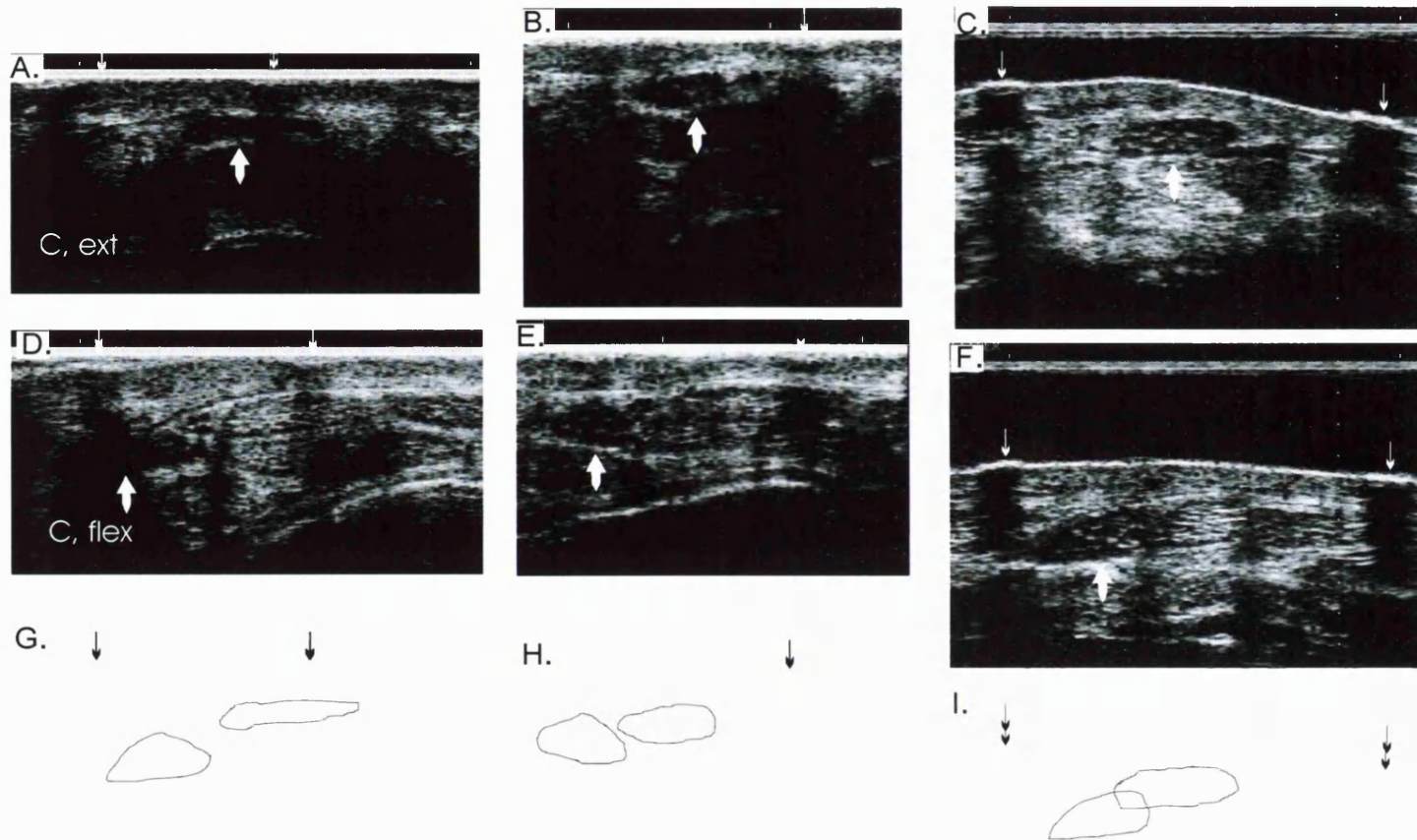


Fig 9.5 Ultrasound images for 3 control subjects with the anterior surface of the wrist to the top and radial direction to the left of the image. First row ( A to C), images in 30 degrees of wrist extension. Surface markers indicated by downward white arrows. Nerve indicated by upward pointing white arrow head. Second row ( D to F), images in 30 degrees wrist flexion. Markers as for first row. Bottom row ( G to I), overlays of the nerve outline and the markers in extension and flexion. Overlays have been positioned to align the markers. Radial movement of the median nerve is clearly demonstrated. Subject on the right was imaged using a 6 mm Sonogel "stand-off" (see methods).

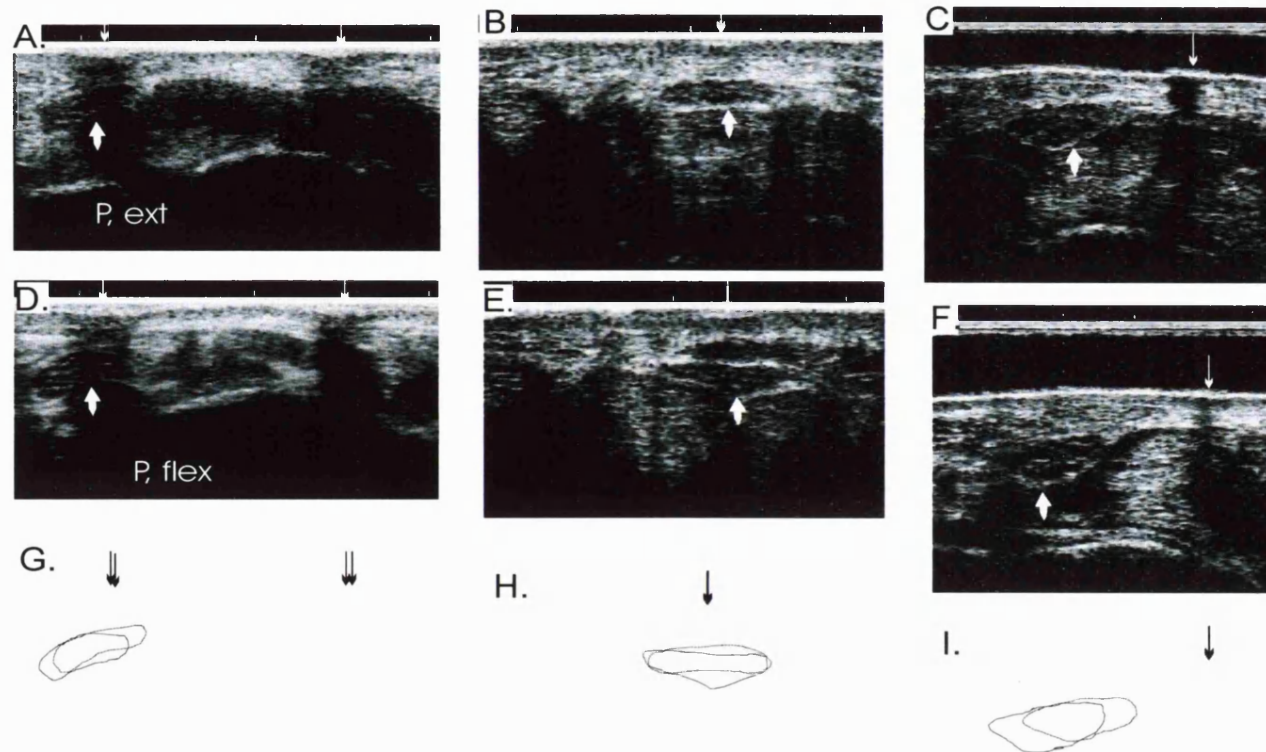


Fig.9.6 Ultra sound images for 3 patients, 2 with severe symptoms and movement restriction on the ULTT1 (left and middle images), one with milder symptoms and ULTT1 graded 1 ( right images). Upper row( A to C), 30 degrees extension, lower row ( D to F), 30 degrees flexion. Surface markers indicated by downward white arrows. Nerve position indicated by upward pointing white arrows. Lower row ( G to I), overlays to show nerve position in flexion and extension relative to surface markers. In neither of the two subjects with severe symptoms did the nerve change position between extension to flexion, in the subject with less severe symptoms there is a small radial movement of the nerve on flexion. Images on the right were made using a 6mm sonogel stand-off (see methods).



### 9.3.2 Non specific arm pain patients

In the patient group there was a mean ulnar to radial translation of the median nerve on wrist flexion of  $1.17 \pm 0.51$  mm and the range was from  $-1.01$  to  $+4.06$  mm (see Figs 9.5 and 9.6). These changes were significantly less than in the control subjects ( $p < 0.001$ ) (see Fig 9.7). The depth of the nerve from the ventral surface with the wrist in extension was  $2.75 \pm 0.22$  mm, very similar to the figure for control subjects. The depth in flexion was less at  $3.6 \pm 0.25$  mm and the change in depth between extension and flexion was  $0.92 \pm 0.24$  mm, significantly less than the control group ( $p = 0.02$ ). In the patient group the nerve area averaged  $7.6 \pm 0.4$  mm<sup>2</sup> (3.89-10.85) while the aspect ratio averaged  $2.7 \pm 0.25$  mm<sup>2</sup> (1.4-4.6). These values are not significantly different from the controls.

### 9.4 Repeatability

Four subjects (both patient and control) were measured twice on the same day at an interval of between 1–6 hours. The average difference between repeat measurements of nerve movement during wrist extension to wrist flexion was  $-0.2$  mm (1.0 mm SD). Re-tests on five subjects at an interval of 1 - 2 days showed slightly more variability, average  $-0.03$  mm (1.88 mm SD), but still much less than the overall difference between patients and controls.

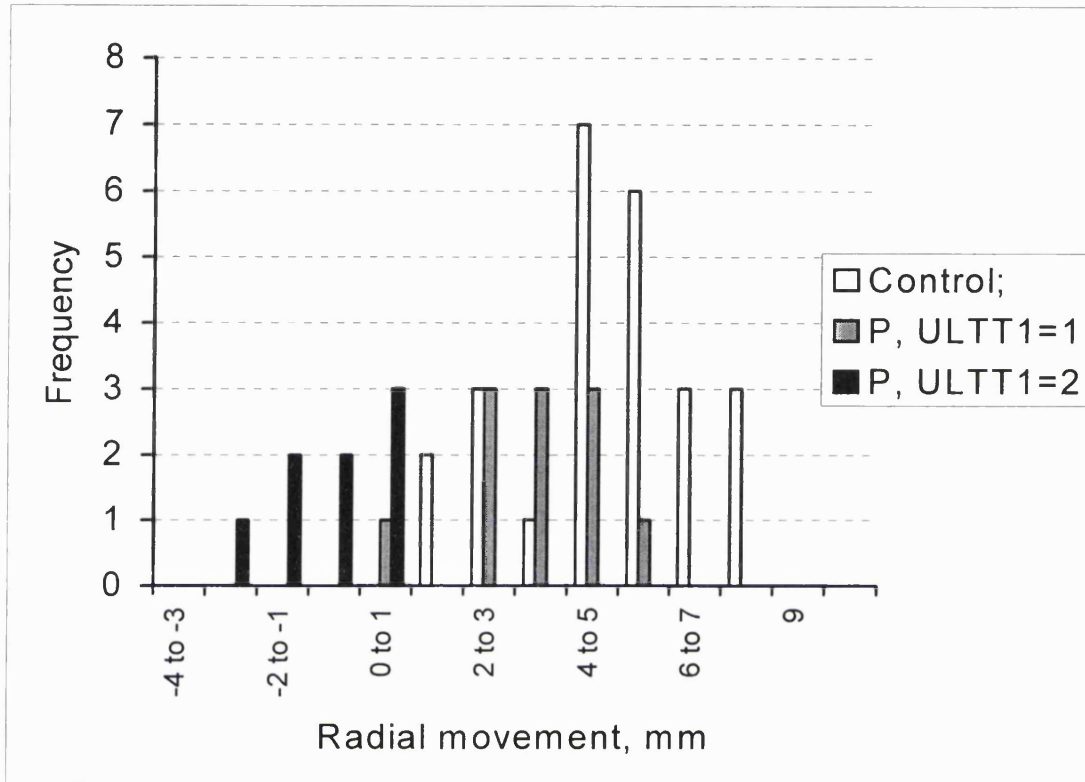


Fig. 9.7. Histogram showing average radial movement on taking wrist from 30° extension to 30° flexion in 25 wrists in 16 control subjects and in 19 wrists in 12 patients with NSAP. ULTT1=2, wrists in arms with score of 2 on upper limb tension test 1 (ULTT1). ULTT1=1, wrists in arms with score of 1 on ULTT1. For explanation of test scores see Methods section.

## 9.5 Median nerve movement and ULTT1

All the patients scored 1 or 2 on testing the ULTT1 on their symptomatic sides (Table 9.1). Three patients scored 0 for their non symptomatic arms . These asymptomatic wrists showed a mean ulnar to radial direction of nerve movement of  $4.95 \pm 0.67$ mm, range 4.02-6.25mm, close to the control average. Patients who scored 1 on the ULTT1 test (8 patients, 11 wrists) had significantly less nerve movement than controls, mean nerve movement  $2.56 \pm 0.41$ mm, range -0.03 to 4.76 mm ( $p=0.001$ ) There was even less movement of the median nerve in the wrists of patients scoring 2 on the ULTT1 (7 patients, 8 wrists) (Fig 30). Mean movement of the nerve in these patients was  $-0.85 \pm 0.45$  mm, range -2.99 to 0.48mm, significantly less than the average for wrists where the ULTT1 was scored 1 ( $p<0.001$ ) (see Fig 9.7). The mean antero-posterior movement of the nerve in patients scoring 1 on ULTT1 was again significantly less than the antero-posterior movement in control subjects, mean  $1.23 \pm 0.29$  mm, range 0.48-3.80 ( $p<0.05$ ). Patients scoring 2 on ULTT1 had even less movement, compared to control subjects, mean  $0.30 \pm 0.25$ mm, range -0.80 to 1.52. Again these values were significantly less than for patients scoring 1 on ULTT1 ( $p<0.05$ ).

## 9.6 Discussion

In this study we have used high resolution ultrasound imaging to measure the movement of the median nerve in the wrist just proximal to the carpal tunnel during wrist movement from 30°extension to 30°flexion. Both transverse and antero-posterior movement of the median nerve in patients with non-specific arm pain was significantly reduced compared to an age matched control group, and this is in agreement with previous work using MRI.

Further, it is clear that median nerve movement assessed using a clinical test of neural dynamics, ULTT1, correlates significantly with the extent of nerve movement measured from ultrasound images.

There is good overall agreement between the values for nerve movement observed here and those reported using MRI . Using MRI, the mean radial movement on flexion in 8 female control subjects was  $3.2 \pm 0.50$ mm compared with  $4.5 \pm 0.67$  mm for 13 female controls in this study and the mean radial movement in patients using MRI was  $1.0 \pm 0.64$ mm compared with  $1.2 \pm 0.51$ mm reported here.

Lack of nerve movement in the patients could be a reflection of decreased use of the painful limb. Nerve movement has been examined in one subject with painful symptoms due to extensor tenosynovitis, and was above the control average at 6.17 mm. This result would suggest that disuse is not a major factor in the development of reduced nerve mobility. It should also be noted that for the most part the patient group did use their upper limbs for many functional activities, although keyboard use and gripping were often restricted due to pain.

The extent to which median nerve entrapment at the carpal tunnel contributes to NSAP needs to be considered. Movement of the median nerve in our patients was restricted and this has been observed in patients with carpal tunnel syndrome (Allman et al. 1997). Nerve area and aspect ratios found in our control subjects are close to the values reported recently in a large study using high frequency ultrasound to image the proximal carpal tunnel (Duncan et al. 1999). Duncan et al. (1999), also reported a greatly increased nerve area (by 80%) in patients with carpal tunnel syndrome. However no

similar swelling was seen in our group of NSAP patients. This, combined with the diffuse nature of reported symptoms, plus a general lack of response to both steroid injection and wrist splinting in the NSAP patients (Arksey, 1998, Reilly, 1993) leads us to the view that these patients are unlikely to have nerve entrapment restricted to this one site.

In conclusion, this study has shown that ultrasound imaging can provide a way of assessing movement of the median nerve in the carpal tunnel on wrist flexion and extension. The transverse and antero-posterior movement of the nerve is much reduced in patients with NSAP. Ultrasound imaging should be considered in the diagnosis of this condition and may also provide a cost-effective way of assessing the outcome of different treatments.

## **9.7 Criticism of methodology**

1. A concern with the ultrasound measurements was the degree of repeatability. There are a number of ways in which inaccuracies may occur. For example, it is clearly important that the position of the scanner and the angle of the ultrasound beam to the nerve do not differ markedly between successive measurements. Care was taken to keep the ultrasound probe at the same level on the wrist for all trials, but small variations of up to 3 mm between scans cannot be excluded. The course of the nerve in the wrist is parallel to the long axis of the limb, so it is unlikely that estimates of radial-ulnar movements will be affected significantly. However, the estimates of nerve depth may be affected, and these are also subject to error if the

ultrasound beam is not maintained at the same angle to the nerve. In general, these geometrical errors are probably small given the anatomy of the nerve at the wrist and its very superficial location (within 2-5 mm of the surface in most subjects).

Certainly, the errors in the measurements are not enough to obscure a clear difference between the patient and control group.

## Chapter 10: Discussion

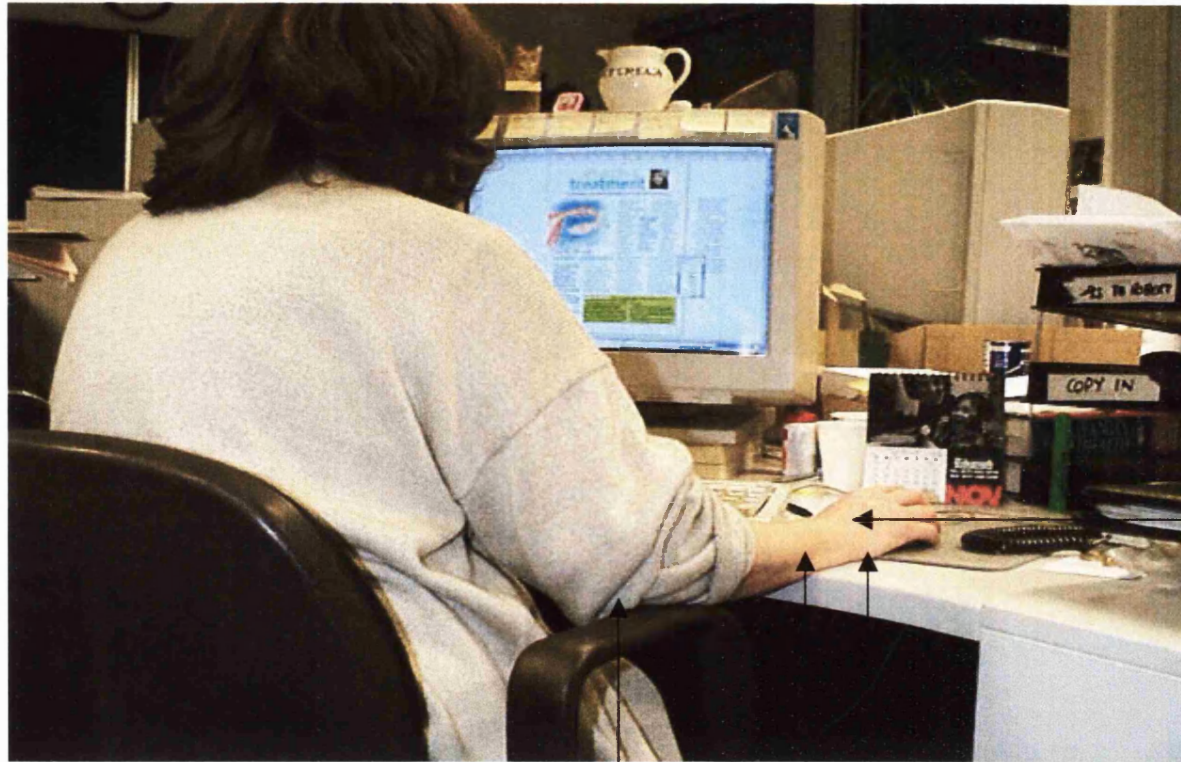
RSI patients present with diffuse, chronic arm pain that is often associated with paraesthesia. Patients also report allodynic responses to both mechanical stimulation, as demonstrated in our study on vibration sensitivity and to electrical stimulation as reported by Arroyo and Cohen (1992). Patients do not demonstrate obvious signs of tissue inflammation, discrete symptoms of single nerve entrapment syndromes or slowing of nerve conduction velocity. As such they present a considerable clinical problem both for diagnosis and effective treatment. Hendlar (1996), suggests that when clinicians are unable to explain symptoms using standard medical tests then the tendency may be to explain symptoms in terms of a psychological disturbance. There is no evidence to suggest that patients with RSI have psychological problems prior to the occurrence of symptoms (Spence 1998). However in common with many chronic pain patients, depression and anxiety are likely to be factors in their overall presentation (Spence 1987).

The hypothesis presented at the end of Chapter 2 (Fig 2.3), suggesting that RSI patients do have a neuropathic basis for their symptoms, can now be addressed. Is it plausible that keyboard use could adversely affect the neural environment such that significant neuropathic symptoms could occur without obvious sign of nerve injury? The following section will present evidence that this is indeed likely. I will also examine the cause and clinical consequences of reduced nerve mobility observed in these patients.

## **10.1 Can the mechanical stresses associated with keyboard use affect peripheral nerve function?**

Fig. 10.1 depicts a common posture adopted by office workers. This posture, assumed for many hours, is associated with prolonged changes in muscle tension particularly around the neck, shoulder girdle region and forearm musculature. Sustained or repetitive contraction of muscles, where these are anatomically closely associated with peripheral nerves, may cause an increase in local pressure or friction. The repetitive or static holding of non neutral joint positions, defined here as a joint held beyond its mid range point, may place nerve trunks at risk of compressive and frictional forces from fibro-oseous tunnels and adjacent soft tissue. For example the ulnar nerve becomes more closely associated with the medial epicondyle of the humerus with elbow flexion, while pressure around the nerve increases at the cubital fossa with increasing elbow flexion (Okamoto et al 2000, Gelberman et al.1998, Pechan and Julis 1975). When tissues are subject to load and pressure the pressure gradients formed will redistribute the compressed tissue to an area of lower pressure gradients. Sites where a nerve passes through a narrow fibrous-osseous tunnel or where stiff tissue forms a tunnel boundary are areas where nerves are at increased risk of compression ( Remple 1999). Fig. 10.2 outlines the path of the median nerve and identifies possible sites of compression. Sustained muscle activity ( for example, finger flexor muscles and pronator), wrist extension and direct pressure over the carpal tunnel associated with keyboard use (see Fig 10.1), may over time change the neural environment at several of these sites as outlined below.





Carpal tunnel /  
median nerve

Guyon's canal / ulnar nerve

Pronator muscle / median nerve

Cubital fossa / ulnar nerve

Fig.10.1 Typical office worker posture indicating possible anatomical sites of peripheral nerve compression

The propagation of nerve impulses and the flow of axoplasm requires an adequate blood supply. Interference with neural venular flow of rabbit tibial nerves has been observed at pressures of 20 mmHg, arteriolar and intrafascicular flow being reduced at 40 – 50 mmHg ( Rydevik et al. 1981). Neural oedema due to increased vascular permeability has been observed following compression at low pressures (40mmHg). Elevated endoneurial pressure after eight hours of external compression at 40 mmHg resulting in reduced endoneurial blood flow (Rydevik and Lundborg 1977). Interestingly pressures of these magnitudes have been recorded within the carpal tunnel of patients with CTS (Gelberman 1981) and have also been recorded in the carpal tunnel in asymptomatic subjects during wrist extension, flexion, and finger flexion (Keir et al. 1998), all positions that are required for typing on keyboards. Pressures of between 20 - 33 mmHg have been recorded within the carpal tunnel of asymptomatic subjects during computer mouse use (Remple 1999). Elevated vibration thresholds have been recorded in healthy volunteers following 40mmHg median nerve compression applied for four hours (Gelberman et al. 1983). In our patient group there is clear evidence of elevated vibration thresholds. In these patients fascicular and endoneurial vessel damage may have reached a critical stage. Arm, wrist position and muscle activity involved with keyboard operation may further compromise neural blood flow, as outlined above, such that impulse propagation is diminished. As observed by Dellon (1980), A $\beta$  fibres are most sensitive to

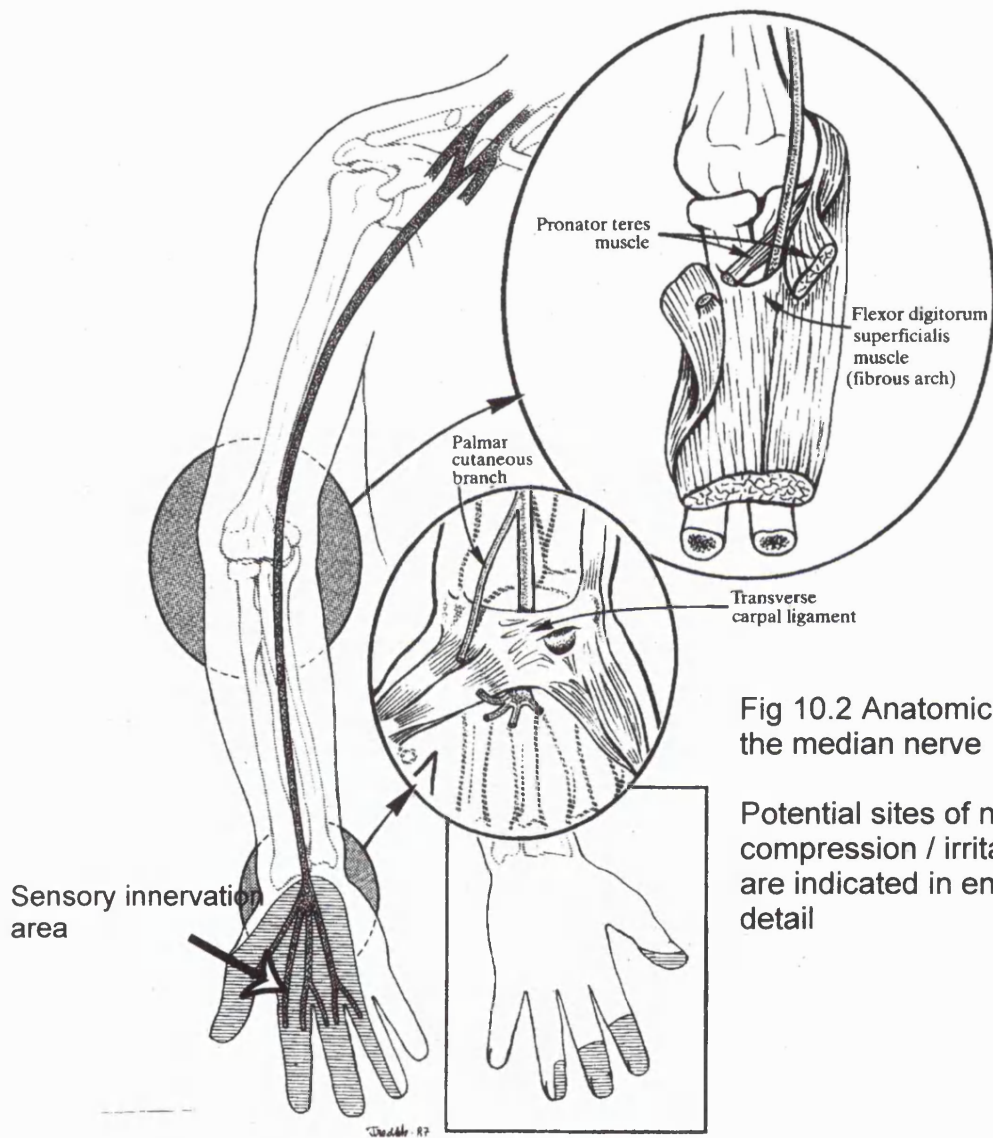


Fig 10.2 Anatomical track of the median nerve

Potential sites of nerve compression / irritation are indicated in enlarged detail

Adapted from Lundborg 1988

ischaemia and elevated vibration threshold may precede change to nerve conduction velocity as an indication of changed nerve fibre function.

As discussed in Chapter 2 (2.3.2), changes to axoplasmic flow have been observed with relatively small increases in pressure (20 –30mmHg) around a nerve trunk. Crucially the time for which these pressures are applied appears important for producing changes in axoplasmic flow. Thus Dahlin and McLean (1986) found that 20-30 mmHg pressure applied to a rabbits sciatic nerve for 8 hours resulted in the inhibition of fast and slow axonal transport whereas 20mmHg for only two hours had no significant effect. The sustained postures typical of intensive keyboard use may be associated with prolonged elevated pressures around peripheral nerves and, as observed experimentally, lead to a change in axoplasmic flow. As previously described, this will have consequences for both the transport of neurotrophins, and the synthesis of neurotransmitters. The ability of the nerve to repair itself following injury will be reduced since transport of cytoskeletal elements to distal parts of the axon as well as the retrograde flow of trophic factors may be lowered (Lundborg 1988).

### **10.1.1 The double crush phenomenon**

Reduced axoplasmic flow has been suggested as the basis for the “double crush phenomenon” where proximal nerve compression renders the distal portions of the nerve more vulnerable to compressive forces. Upton and McComas (1973) observed that 70% of 115 patients with either carpal tunnel syndrome (CTS) or ulnar (cubital tunnel) neuropathy had evidence of cervico-thoracic root lesions. The term “double crush” was introduced to suggest that sites of impingement along a nerve trunk, not sufficient by themselves to cause symptoms, may cumulatively cause an entrapment syndrome. The authors also observed an association between CTS and ulnar nerve

compression at the elbow, calling this “multiple entrapment neuropathy”.

Interestingly the authors speculate that proximal nerve “stretch” due to nerve tethering may render the distal portions of the nerve more susceptible to nerve compression. Clinical observations and animal experiments tend to support this hypothesis. Dellon and MacKinnon (1991), demonstrated that a single site of minimal sciatic nerve compression resulted in a progressive deterioration in the amplitude of the compound action potential over a period of 5 months. The amplitude of the compound action potential measured in rats with double banded sites of compression was significantly worse than the single banded group four months after banding. Interestingly the degree of electrophysiological dysfunction reached a plateau by 7 months following this minimal degree of nerve compression. The amplitude of the compound action potential in a group of rats with single nerve banding decreased rapidly following the addition of either another proximal or distal compression site. Within 3 months the action potential had reached the same level as the initially double banded group. Nemoto et al. (1987), studied the double crush phenomenon by means of compression clamps on canine sciatic nerves. Partial conduction block and mild (A $\beta$  fibre) axonal degeneration was induced by a single compression, however following the application of a further compression site loss of nerve function was greater than the sum of the deficits after each separate compression. The pressure forces under the clamps, measured and over the 8 weeks that they were applied, were on average 25 mmHg. Hurst et al. (1985), made a statistical analysis of 888 patients with carpal tunnel syndrome and found a strong association with cervical spondylosis and bilateral carpal tunnel syndrome. They suggest that cervical spondylosis causing mild proximal nerve impingement in combination with mild CTS caused symptoms that would not be present if either condition was acting alone. Richardson et al. (1999) looked for electrophysiological evidence of median sensory mono neuropathy with C6/7 radiculopathy cases and motor neuropathy for C8

radiculopathy cases. They found an unexpected increased incidence (22%) of sensory median mononeuropathy at the wrist in all cases of cervical radiculopathy. The authors conclude that these results do not support the double crush hypothesis since the distribution of median neuropathy was not consistent with the level of cervical root lesion (C8 cases demonstrating the same frequency of sensory defined median neuropathy as C6). However it is still unknown whether nerve fibres most susceptible to compression at one site might or might not be those most vulnerable at another site. Further the authors do not appear to consider that this particular form of double crush may occur distal to proximal rather than vice versa, a condition referred to as "reversed double crush syndrome" (Lundborg 1988).

### **10.1.2 Nociceptor function and dorsal horn excitability following nerve injury**

Recent physiological work has shown that nerve compression or irritation will trigger marked changes in normal function and pain behaviour (Bennett 1988). In the CCI model, nerve injury will cause altered C fibre firing (Koltzenburg 1994a). Ectopic firing of C fibres both in the periphery and at sites of trauma along the nerve trunk triggers a cascade of events within the central nervous system that include increased central excitability, leading to chronic pain (McMahon 1993, Devor 1988).

Nerve inflammation may cause change to the blood nerve barrier and allow cytokine access to the nerve fibre environment and induce ectopic C fibre activity (Sorkin et al. 1997). These changes have been observed following nerve sheath inflammation without evidence of axonal degeneration and can lead to neuropathic symptoms and allodynic responses (Eliave 1999). Similar changes to the blood nerve barrier, without axonal degeneration, in the presence of neuropathic symptoms, has been observed in patients with minor nerve injury (Mackinnon et al. 1986).

Nerve sheath innervation includes sensory C fibres (Bove 1995, Zochodne and Ho 1993, Zochodne 1993). Inflammation of the nerve sheath will occur following friction or compression. Local elevation of levels of NGF, and other inflammatory mediators such as bradykinin, and serotonin may sensitise these nociceptors ( Koltzenburg et al 1999). While the contribution that the nervi nervorum may make to dorsal horn neuronal excitability remain to be evaluated, nerve trunk hyperalgesia may occur (Bove 1997). Hyperalgesia on nerve trunk palpation is a common feature in RSI patients (Hall 1999).

Neural inflammatory/compressive injuries such as the CCI model are associated with extensive alteration to neurotrophin levels. This has consequences for neuropeptide expression in C fibres, and possibly A $\beta$  fibres. Altered levels of neurotrophin in the dorsal horn are also reported. These biochemical changes lead to novel synaptic connections and cause increased neuronal excitability at the dorsal horn promoting chronic pain and centrally mediated allodynic responses (Malcangio et al. 2000, Mannion et al. 1999, McMahon et al. 1997, Jenkins et al. 1993, McMahon 1993, Devor 1988, Cook et al. 1987). As described in the Introduction (1.5), chronic pain and allodynia are key features in RSI patients.

In summary, the postures and repetitive muscle activity associated with intensive keyboard work appear capable of causing change to the neuronal environment. There is accumulating evidence that such changes can lead to significant alteration in nerve function and these changes may lead to pain symptoms and altered sensory responses. It is also worth noting that the inherent susceptibility of nerves to injury appears to be in part genetically determined (Mogil et al. 1999, Shir et al. 1990) and make it likely that only a certain proportion of people engaged in the same task will experience RSI.

## 10.2 Nerve mobility

As described in the Introduction (1.5), painful response and loss of normal range of joint movement are reported when test of neural mobility are examined in RSI patients (Byng 1997). Such a response was apparent when the ULTT1 was tested in the patient group examined as part of these studies. In both imaging studies severity of response to the ULTT1 corresponds well with the extent of nerve movement measured objectively.

The nerve movement imaging studies do not identify the reasons for, or all possible sites of reduced median nerve movement. However as reported by Sommer et al. (1993), and Mosconi et al. (1996), inflammation of the nerve sheath caused by irritation or compression will lead to fibrosis and the nerve may become adherent to surrounding musculature. At the carpal tunnel this may be due to inflammatory adhesions between the median nerve and the finger flexor tendons. Fibrosis of the nerve will have detrimental effects on nerve gliding. Loss of nerve movement in turn will lead to increased mechanical forces being exerted on the nerve during joint movement causing further micro trauma and inflammation (Lundborg 1988). Increased tension on a segment of nerve may impair nerve blood flow (Remple et al. 1999), and loss of nerve movement may also place the nerve at increased risk of compression from adjacent moving tissue, for example, the flexor tendons at the carpal tunnel. The median nerve in the carpal tunnel is closely associated with the finger flexor tendons. With wrist flexion nerve translation in a radial direction is a consistent feature of the control group in both the ultra sound and MRI studies. Radial translation appears likely to reduce the stress applied to the nerve by the anterior movement of the flexor tendons occurring with wrist flexion. Note that this may also happen when only the fingers are flexed and the wrist remains in a neutral position (Bay et al. 1997, Nakamichi and Tachibana 1995) such as occurs with keyboard use and with gripping activities. It is important to remember that nerve movement occurs in all planes, i.e. longitudinally, medial



to lateral and antero posterior. A lack of longitudinal sliding of the median nerve will cause extra stress to the nerve during all hand movements, including wrist extension.

Patients with RSI experience marked pain when using computer keyboards. In the presence of nerve injury the application of mechanical stress will lead to prolonged and abnormal nerve fibre firing (Devor 1994). This may include sensitised nerve fibres present within an inflamed nerve sheath. Wright et al. (1997), demonstrated that the arm position associated with typing produced maximal distal excursion of the median nerve. If normal nerve gliding is impaired this posture is likely to produce mechanical stresses of a higher magnitude than would occur with other arm movement and postures.

### **10.2.1 Nerve movement on video**

During our investigation with ultrasound imaging we had the opportunity to video the proximal carpal tunnel during typing. It became clear that the carpal tunnel is a lively place during keyboard typing, the flexor tendons are in rapid motion and the median nerve makes repeated rapid adjustments of its position to accommodate these tendon movements. It is easy to see that any restriction of the ability of the nerve to move would lead to increased stresses. In susceptible individuals, e.g. those with slightly narrower than average carpal tunnels, these stresses would in turn lead to minor nerve injury or to excitation of the nervi nervorum.

### **10.3 Summary**

Keyboard use involving sustained arm positions and repetitive muscle activity may lead nerve injury. On the basis of the "double crush phenomenon" nerve injury may occur at various sites along a nerve track or occur in multiple nerves where the nerve is narrowly constrained within fibrous osseous tunnels or is closely associated with actively contracting muscles. The consequences of nerve injury appear to be extensive. Such injuries may lead to significant pain and altered sensory responses

as demonstrated in this patient group. For patients presenting with multiple sites of minor nerve injury and diffuse symptoms diagnosis may be difficult. Electrodiagnostic tests may be normal since fascicular damage is not extensive. However as these results show, changed nerve function may be demonstrated with vibration threshold testing. Further, painful response to tests of nerve dynamics have been demonstrated in this patient group, and as our results on neural imaging show, a restriction of median nerve mobility can be clearly demonstrated.

#### **10.4. RSI and carpal tunnel Syndrome**

In Chapter 1 (1.6.4) I refer to the similarity between certain features of RSI and carpal tunnel syndrome (CTS). These studies have identified dysfunction of the median nerve and it may be argued that these patients have carpal tunnel syndrome (CTS). CTS, compression of the median nerve at the carpal tunnel, is one of the most frequently diagnosed nerve compression syndrome of the upper limb and has been the most intensively investigated. Patients complain of numbness, paraesthesia and pain in the radial half of the hand and fingers which is frequently worse at night or following hand activities. CTS is said to occur in the fifth and sixth decades of life, is more likely to involve the dominant hand and to affect women more frequently than men (Greenspan 1998). It may be caused by bony hypertrophy, inflammation of the flexor tendons and as a consequence the vascular and joint changes associated with rheumatoid arthritis. Increased incidence of CTS has been observed during pregnancy, diabetes, nephrotic syndrome and obesity. Space occupying lesions such as amyloidosis, gout, tumour and aberrant muscles and arteries can occur in the carpal tunnel (Spindler and Dellon 1982) leading to compression of the median nerve. Frequently CTS is idiopathic, however there is some evidence that median nerve ischaemia and compression at the carpal tunnel are occurring and that these can be caused by repetitive wrist and finger movement, high finger loading forces,

non neutral joint positions and vibration (Dennerlien et al. 1998, Stromberg et al. 1997, Werner et al. 1997, Remple et al. 1997).

Diagnostic criteria based on clinical findings and slowing of median nerve conduction velocity have been suggested for CTS (Harrington 1998, Remple et al. 1998).

Subjective criteria are; symptoms of pain, tingling or numbness in the median distribution in the hand and positive sensory findings on Phalens test (Phalen 1966), (sustained wrist flexion for 30 seconds) and on Tinel's test (tapping over the median nerve in the carpal tunnel). If strict diagnostic criteria for CTS are applied, i.e. specific pain referral and abnormalities of nerve conduction, then RSI patients certainly do not have CTS. Indeed none of the patients screened prior to inclusion into these studies had symptoms restricted to just the median nerve distribution in the hand or positive responses either to Tinel's test or Phalens test position. Further, unlike mild CTS which may present without abnormal conduction studies (Dawson 1993), RSI patients do not respond to carpal tunnel steroid injection and wrist splinting (Arksey 1998, Reilly 1993). Given the now strong evidence for the work relatedness of CTS the obvious question is why don't RSI patients have CTS? The answer may be that they do have mild CTS, but only as part of the overall neural pathology. In the vibration study the patient group had elevated thresholds for the ulnar nerve as well as the median nerve, and as indicated in Fig 10.1, the particular postures associated with keyboard work may subject all three peripheral nerves in the upper limb to compressive forces at multiple sites. The cumulative effect of multiple sites of minor nerve entrapment may explain the diffuse symptoms described by RSI patients and mean that treatment directed to just one site of nerve entrapment is likely to be ineffective.

## **10.5 Treatment**

A comprehensive musculoskeletal examination is of primary importance to exclude conditions with clear pathology, e.g. tenosynovitis, epicondylitis or carpal tunnel syndrome. Note that these conditions may co-exist with RSI. Treatment outcomes for RSI have not been evaluated systematically. On the whole these patients do not respond to rest, non-steroidal anti-inflammatory drugs, or splinting. In a diffuse condition like RSI, surgery is seldom attempted and outcomes are not reported to be very satisfactory (e.g. see Terrono and Millender, 1996). Response to expert physiotherapy has been reported as successful (Arksey 1995), but is not always advocated (Hagberg 1996). Many authors (Nainzadeh 1999, Melhorn 1998; Keller et al. 1998) advise a multidisciplinary approach. This includes physiotherapy, acupuncture, modification of work tasks, ergonomic intervention, and participation in chronic pain management programs. Patient education explaining the postural mechanisms that produce symptoms and self-help methods for avoiding symptom aggravation are essential. Unless early intervention is possible, treatment tends to be prolonged and patients rarely return full time to occupations that involve intensive hand use.

## **10.6 Prevention**

There appears to be sufficient information linking intensive repetitive work with CTS (Viikari-Juntura and Silverstein 1999), however a clear causal relationship between RSI and repetitive work remains unproven. This may be due to difficulties both in nomenclature and diagnosis plus the absence of longitudinal studies. However there does appear to be an association between highly repetitive tasks and RSI (NOHSC 1986). As with work related CTS careful attention to working conditions should help

eliminate some of the risks (Melhorn 1999). Thus those doing regular keyboard or mouse use should have ergonomically sound workstations and should take regular breaks (Health and Safety Executive UK 1992). Maintaining flexibility with regular exercise also appears worthwhile in those with occupations that are mainly sedentary. A working environment that allows for individual control over rate and variation of work tasks would be helpful (Bernard 1994). This approach needs to be linked to an effective programme to pick up problems early, when they are most easily treated. Limb pain, numbness or tingling are signs to look out for, and should not be ignored. Clearly while it is important not to incite exaggerated responses to minor aches, a working environment that encourages the early reporting of symptoms is an advantage.

## **10.7 Conclusion**

When examined in a more extensive fashion than the standard medical models, patients with RSI demonstrate clear signs of peripheral and central neural functional change. It appears that nerves and their blood supply may be critically exposed to friction, compression and traction forces during repetitive movements associated with computer keyboard use and while these factors may have little effect over short periods, prolonged exposure may lead to significant changes in nerve function. These results demonstrate that patients with RSI do have a neuropathic cause for their symptoms. The elevated vibration thresholds, particularly affecting the median nerve but also affecting the ulnar nerve, suggest that they have a mild neuropathy. Allodynic responses reported by these patients following suprathreshold vibration stimulation also suggest that they have alteration to central sensory processing. It is clear from the imaging studies that the normal dynamics of the median nerve associated with wrist flexion and extension are altered in this patient group and this may be a further source of nerve dysfunction and pain. Finally the nerve movement

results fit well with those observed from the patient group for a clinical test of nerve movement (ULTT1).

Clinical evaluation which includes use of ULTT1 combined with MRI or ultrasound images of the carpal tunnel in wrist flexion and extension, with measurement of median nerve mobility could prove useful in the diagnosis and evaluation of treatment protocols in non-specific arm pain.

Early and appropriate treatment that addresses the problems provoked by sustained poor posture and repetitive hand activities should lead to a more favourable prognosis. As with any condition that has the potential to develop into a chronic pain problem, prevention is the most desirable course of action and future studies that identify those most at risk of developing this condition are urgently required.

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**THE MIDDLESEX HOSPITAL**

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Fax: .....

**MRI. CHECKLIST**

SURNAME:.....FORENAME:.....

DATE OF BIRTH:.....

HEIGHT:.....WEIGHT:.....

*It is important, for your safety, that you read carefully and answer fully, all the questions below by circling YES or no.*

**DO YOU HAVE:**

- 1. A pacemaker YES/no
- 2. An artificial heart valve. YES/no
- 3. Surgical clips in your head YES/no
- 4. Cochlear implants YES/no
- 5. Metal implants YES/no eg. Bone or joint replacements, Harrington rods, embolization coils or sutures

**HAVE YOU EVER HAD:**

- 6. Metallic fragments in your eyes YES/no
- 7. Shrapnel or loose metal fragments in the skin YES/no
- 8. Surgery to the head, heart or spine YES/no

**FOR WOMEN OF CHILD BEARING AGE.**

- 9. Is there any possibility that you may be pregnant? YES/no
- 10. Are you breast feeding? YES/no

**BEFORE GOING INTO THE MRI SCANNER :**

**ENSURE THAT YOU HAVE REMOVED WATCHES, MAGNETIC SWIPE CARDS e.g. BANK/CREDIT CARDS, TUBE/RAIL TICKETS AND ANY LOOSE METALLIC OBJECTS e.g. COINS/JEWELLERY**

PATIENT/GUARDIAN SIGNATURE:.....PRINT NAME:.....

SIGNATURE OF RADIOGRAPHER:.....DATE:.....



**The University College London Hospitals**

University College London Hospitals is an NHS Trust incorporating The Eastman Dental Hospital, The Hospital for Tropical Diseases, The Middlesex Hospital, The National Hospital for Neurology & Neurosurgery, The United Elizabeth Garrett Anderson Hospital and Hospital for Women, Soho, and University College Hospital.

# APPENDIX II CLINICAL ASSESSMENT PROTOCOL

## PATIENT/ OFFICE WORKER / CONTROL SUBJECT INFORMATION

AGE:.....(yrs)

SEX: M.

F.

Dominant Hand :

R.

L.

either.

Hobbies .....

Regular sports .....

### HISTORY-

Past symptoms

Y.

N.

Current Symptoms

Y.

N.

Treatment

Y.

N.

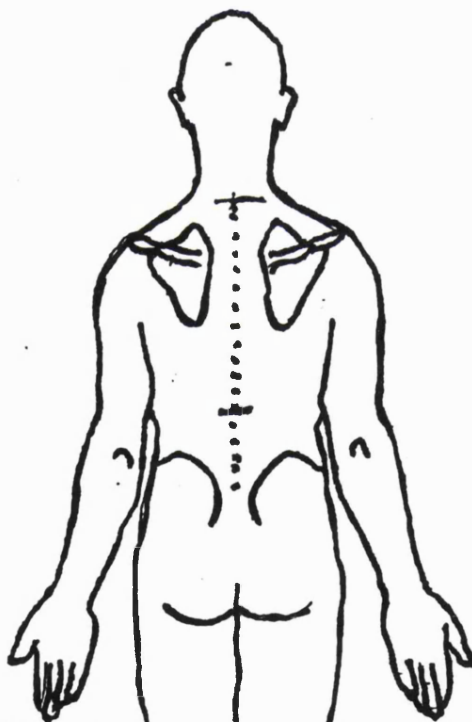
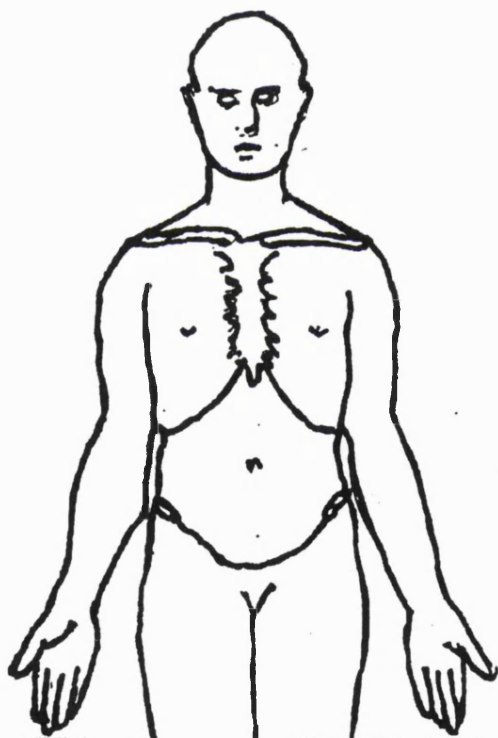
Length of time of current sympt..... days/ weeks/ months

Subjective sensory changes

Y.

N.

Hx onset:



CATEGORY P  O/W  C

STUDY L  C/S

CODE:

DATE: \_\_/\_\_/00

No symptoms

Worst imaginable

**WORK INFORMATION**

**WORKING TASKS:**

Use of DSE ≥ 40% of working week      Y.     N.

**WORK HISTORY:**

Job Title .....

Number of years / months using DSE .....

**SPECIAL QUESTIONS :**

Diabetic	0. <input type="checkbox"/>	1. <input type="checkbox"/>
Pregnancy	0. <input type="checkbox"/>	1. <input type="checkbox"/>
Menopausal	0. <input type="checkbox"/>	1. <input type="checkbox"/>
Obvious trauma - pre sympt. :		
Whiplash, # U/L	0. <input type="checkbox"/>	1. <input type="checkbox"/>
Neuro - MS etc	0. <input type="checkbox"/>	1. <input type="checkbox"/>

Relevant Familial Hx      0.       1.  .....

Any exposure to: solvents

Lead, organophosphates      0.       1.  .....

**MANAGEMENT OF SYMPTOMS**

**COMMENTS**

Physio	0. <input type="checkbox"/>	1. <input type="checkbox"/>
Chiroprac	0. <input type="checkbox"/>	1. <input type="checkbox"/>
Osteopathy	0. <input type="checkbox"/>	1. <input type="checkbox"/>
Drugs	0. <input type="checkbox"/>	1. <input type="checkbox"/>
Injections	0. <input type="checkbox"/>	1. <input type="checkbox"/>
Other.....		

**INVESTIGATIONS**

**RESULTS**

MRI	0. <input type="checkbox"/>	1. <input type="checkbox"/>
Xrays	0. <input type="checkbox"/>	1. <input type="checkbox"/>
Blood Tests	0. <input type="checkbox"/>	1. <input type="checkbox"/>
Nerve Conduct	0. <input type="checkbox"/>	1. <input type="checkbox"/>

KEY : 0 = NO  
1 = YES

CODE:   
DATE: \_\_/\_\_/00



**CERVICAL SPINE / UPPER LIMBS**

**(1) CERVICAL SPINE:**

Rotation (R) (a)	0.□	1.□	2.□	3.□
(L) (b)	0.□	1.□	2.□	3.□
Side Flex (R) (c)	0.□	1.□	2.□	3.□
(L) (d)	0.□	1.□	2.□	3.□
Flexion (e)	0.□	1.□	2.□	3.□
Extension (f)	0.□	1.□	2.□	3.□
Sust. Rot (R) (g)	0.□	1.□	2.□	3.□
10 secs (L) (h)	0.□	1.□	2.□	3.□

**COMMENTS**

**(2) SHOULDER:**

Flexion (R) (a)	0.□	1.□	2.□	3.□
(L) (b)	0.□	1.□	2.□	3.□
Abduct (R) (c)	0.□	1.□	2.□	3.□
(L) (d)	0.□	1.□	2.□	3.□
Lat. Rot (R) (e)	0.□	1.□	2.□	3.□
(L) (f)	0.□	1.□	2.□	3.□
Med. Rot (R) (g)	0.□	1.□	2.□	3.□
(L) (h)	0.□	1.□	2.□	3.□
Ext. (R) (i)	0.□	1.□	2.□	3.□
(L) (j)	0.□	1.□	2.□	3.□
Horiz/Flex(R) (k)	0.□	1.□	2.□	3.□
(L) (l)	0.□	1.□	2.□	3.□

**COMMENTS**

Active

Passive

Active

Passive

Active

Passive

Active

Passive

Active

Passive

**(3) ELBOW:**

Flex (R) (a)	0.□	1.□	2.□	3.□
(L) (b)	0.□	1.□	2.□	3.□
Ext. (R) (c)	0.□	1.□	2.□	3.□
(L) (d)	0.□	1.□	2.□	3.□

**COMMENTS**

KEY 0 = Full mvt. No sympt.  
 1 = Full mvt. with symptoms  
 2 = ↓ mvt. No sympt.  
 3 = ↓ mvt. and sympt. reproduced.

CODE: □□□□□□/□

DATE: \_\_/\_\_/00

**(4) FOREARM:**

Supin.	(R) (a) 0.□	1.□	2.□	3.□
	(L) (b) 0.□	1.□	2.□	3.□
Pron.	(R) (c) 0.□	1.□	2.□	3.□
	(L) (d) 0.□	1.□	2.□	3.□

**COMMENTS****(5) WRIST:**

Flex	(R) (a) 0.□	1.□	2.□	3.□
	(L) (b) 0.□	1.□	2.□	3.□
Ext.	(R) (c) 0.□	1.□	2.□	3.□
	(L) (d) 0.□	1.□	2.□	3.□
R/dev	(R) (e) 0.□	1.□	2.□	3.□
	(L) (f) 0.□	1.□	2.□	3.□
U/dev	(R) (g) 0.□	1.□	2.□	3.□
	(L) (h) 0.□	1.□	2.□	3.□

**COMMENTS****(6) THUMB:**

Add	(R) (a) 0.□	1.□	2.□	3.□
	(L) (b) 0.□	1.□	2.□	3.□
Abd	(R) (c) 0.□	1.□	2.□	3.□
	(L) (d) 0.□	1.□	2.□	3.□
Opp.	(R) (e) 0.□	1.□	2.□	3.□
	(L) (f) 0.□	1.□	2.□	3.□

**COMMENTS**

KEY 0 = Full mvt. No sympt.  
 1 = Full mvt. with symptoms  
 2 = ↓ mvt. No sympt.  
 3 = ↓ mvt. and sympt. reproduced.

CODE: □□□□□□/□

**(7) NEUROLOGICAL EXAMINATION:****COMMENTS**

Reflexes: (R) (a) 0.  1.   
 (L) (b) 0.  1.

## Sensation:

Light.Touch (R) (c) 0.  1.   
 (L) (d) 0.  1.

Pin Prick (R) (e) 0.  1.   
 (L) (f) 0.  1.

Muscle Power (R) (g) 0.  1.   
 (L) (h) 0.  1.

KEY 0 = Signs not present  
 1 = Signs present

**(8) TENDONITIS:****COMMENTS**

Infraspin. (R) (a) 0.  1.   
 (L) (b) 0.  1.

Supraspin. (R) (c) 0.  1.   
 (L) (d) 0.  1.

Subcapularis (R) (e) 0.  1.   
 (L) (f) 0.  1.

Biceps (R) (g) 0.  1.   
 (L) (h) 0.  1.

C. ext. origin (R) (i) 0.  1.   
 (L) (j) 0.  1.

C. flex. origin (R) (k) 0.  1.   
 (L) (l) 0.  1.

**(9) TENOSYNOVITIS WRIST:****COMMENTS**

Extensor (R) (a) 0.  1.   
 (L) (b) 0.  1.

Flexor (R) (c) 0.  1.   
 (L) (d) 0.  1.

DeQuervains (R) (e) 0.  1.   
 (L) (f) 0.  1.

KEY 0 = Signs not present  
 1 = Signs present

CODE: /

DATE: \_\_/ \_\_/ 00

**(10) NEURAL DYNAMICS:**

**COMMENTS**

ULTT 1	(R) (a)	0. <input type="checkbox"/>	1. <input type="checkbox"/>	2. <input type="checkbox"/>
	(L) (b)	0. <input type="checkbox"/>	1. <input type="checkbox"/>	2. <input type="checkbox"/>
ULTT 2 (med)	(R) (c)	0. <input type="checkbox"/>	1. <input type="checkbox"/>	2. <input type="checkbox"/>
	(L) (d)	0. <input type="checkbox"/>	1. <input type="checkbox"/>	2. <input type="checkbox"/>
ULTT 2 (rad)	(R) (e)	0. <input type="checkbox"/>	1. <input type="checkbox"/>	2. <input type="checkbox"/>
	(L) (f)	0. <input type="checkbox"/>	1. <input type="checkbox"/>	2. <input type="checkbox"/>
ULTT 3	(R) (g)	0. <input type="checkbox"/>	1. <input type="checkbox"/>	2. <input type="checkbox"/>
	(L) (h)	0. <input type="checkbox"/>	1. <input type="checkbox"/>	2. <input type="checkbox"/>

KEY 0 = Normal response  
 1 = ↓mvt. No sympt.  
 2 = ↓ mvt. and sympt. reproduced.

**(11) NEURAL PROVOCATION TESTS:**

**COMMENTS**

Thoracic outlet (Roos Test)	(R) (a)	0. <input type="checkbox"/>	1. <input type="checkbox"/>
	(L) (b)	0. <input type="checkbox"/>	1. <input type="checkbox"/>
(Median)FDS	(R) (c)	0. <input type="checkbox"/>	1. <input type="checkbox"/>
	(L) (d)	0. <input type="checkbox"/>	1. <input type="checkbox"/>
(Median)Pronator	(R) (e)	0. <input type="checkbox"/>	1. <input type="checkbox"/>
	(L) (f)	0. <input type="checkbox"/>	1. <input type="checkbox"/>
(Radial)Supinator	(R) (g)	0. <input type="checkbox"/>	1. <input type="checkbox"/>
	(L) (h)	0. <input type="checkbox"/>	1. <input type="checkbox"/>
(Radial)ECRB	(R) (i)	0. <input type="checkbox"/>	1. <input type="checkbox"/>
	(L) (j)	0. <input type="checkbox"/>	1. <input type="checkbox"/>
(Ulnar)FCU	(R) (k)	0. <input type="checkbox"/>	1. <input type="checkbox"/>
	(L) (l)	0. <input type="checkbox"/>	1. <input type="checkbox"/>

KEY 0 = Signs not present  
 1 = Signs present

**(12) WRIST MEASUREMENT:**

Lat Pisiform - Med Scaphoid (R) .....  
 (L) .....

CODE:   
 \_\_/\_\_/00

**(13) PALPATION:****COMMENTS**

## Supraclavicular Fossa

Tinels	(R) (a)	0.□	1.□
	(L) (b)	0.□	1.□
Shoulder	Acomio-clavicular joint line		
	(R) (c)	0.□	1.□
	(L) (d)	0.□	1.□
	Sub-acromial bursa		
	(R) (e)	0.□	1.□
	(L) (f)	0.□	1.□

## RADIAL NERVE

Superficial	(R) (g)	0.□	1.□
+/- U.D	(L) (h)	0.□	1.□
Rad. Tunnel	(R) (i)	0.□	1.□
	(L) (j)	0.□	1.□
Tinels	(R) (k)	0.□	1.□
	(L) (l)	0.□	1.□

## ULNAR NERVE

Prox Cubital fossa	(R) (m)	0.□	1.□
+/- Elb. flex	(L) (n)	0.□	1.□
Prox. Guyons canal	(R) (o)	0.□	1.□
	(L) (p)	0.□	1.□
Tinels	(R) (q)	0.□	1.□
	(L) (r)	0.□	1.□

KEY 0 = Signs not present  
1 = Signs present

CODE: □□□□□□/□

DATE: \_\_/\_\_/00

**Q13 (Continued) MEDIAN NERVE**

Phalens	(R) (s)	0.□	1.□
	(L) (t)	0.□	1.□
Rev. Phalen	(R) (u)	0.□	1.□
	(L) (v)	0.□	1.□
Prox C.T	(R) (w)	0.□	1.□
+/- wrist ext	(L) (x)	0.□	1.□
Tinels	(R) (y)	0.□	1.□
	(L) (z)	0.□	1.□
Atrophy of	(R)	0.□	1.□
Thenar em	(L)	0.□	1.□

KEY 0 = Signs not present  
 1 = Signs present

CODE: □□□□□□/□

DATE: \_\_/\_\_/00

**An interpretation algorithm for the “Harrington”Delphi Criteria” examination pro-forma .**

<b>Condition</b>	<b>Criteria</b>
<b>Rotator cuff tendinitis</b>	<ol style="list-style-type: none"> <li>1. Pain in the deltoid region; <i>plus</i></li> <li>2. “3” to Q2c-f and Q8a-d</li> </ol>
<b>Bicipital tendinitis</b>	<ol style="list-style-type: none"> <li>1. Pain in the anterior shoulder area; <i>plus</i></li> <li>2. “3” to 2a-b and “1” to Q8e-f and/ or “3” to Q2i-j</li> </ol>
<b>Shoulder capsulitis</b>	<ol style="list-style-type: none"> <li>1. Pain in the deltoid area. <i>Plus</i></li> <li>2. deficit in active <i>and</i> passive movements for <i>either</i> Q2c-h. The cut points* are: <ul style="list-style-type: none"> <li>&lt; 180° for abduction</li> <li>&lt;90° for external rotation</li> <li>&lt;90° for internal rotation</li> </ul> </li> </ol>
<b>Lateral epicondylitis</b>	<ol style="list-style-type: none"> <li>1 . Pain over the lateral elbow; <i>plus</i></li> <li>2. tenderness over the lateral elbow; <i>plus</i></li> <li>3. and “3”to Q5c-d and “1” to Q8g-h</li> </ol>
<b>Medial epicondylitis</b>	<ol style="list-style-type: none"> <li>1. Pain over the medial elbow; <i>plus</i></li> <li>2. tenderness over the medial elbow <i>plus</i></li> <li>3 and “3”to Q5ca-b and “1” to Q8i-j</li> </ol>
<b>De Quervain’s disease of the wrist</b>	<ol style="list-style-type: none"> <li>1. Pain over the radial wrist; <i>plus</i></li> <li>2.tenderness over the radial wrist; <i>plus</i></li> <li>3 “3” to Q5 g-h and “3” to Q6c-d and “1” to Q9e-f</li> <li>4 Negative response on ULTT2 (radial) test</li> </ol>
<b>Carpal tunnel syndrome</b>	<ol style="list-style-type: none"> <li>1.Pain and parathesia in the median nerve distribution of the hand AND ONE OR MORE OF: positive Tinel’s sign <i>or</i> positive Phalen’s test <i>or</i> motor loss with wasting of the thenar eminence <i>or</i> sensory loss (impairment of light touch and or pin prick in thumb and index but not little finger)</li> <li>2.”2” to Q10a-d</li> </ol>

## Tenosynovitis

1. Pain over any of: the dorsal forearm, palmar forearm, dorsal wrist *or* palmar wrist; *plus*
2. Pain on any of the following resisted isotonic movements: \*radial flexion/extension *or* ulnar flexion/extension of the wrist, finger extension *or* finger flexion.
3. Tender on palpation of tendons  $\pm$  crepitus with active finger or wrist movement

- The cut-points for restricted shoulder movement are taken from: American Medical Association: Guides to the Evaluation of Permanent Impairment (3rd edition). American Medical Association, Chicago. 1988.

## Non specific arm pain

1. Pain *and/ or* paresthesia in the arm in the absence of other specific diagnosis or pathology.
2. Restricted movement with reproduction of symptoms with one or more upper limb tension tests
3. Pain *and / or* paresthesia on palpation of one or more of the peripheral nerve trunks
4. May also complain of loss of arm/hand function, muscle weakness without muscle atrophy, muscle tenderness, allodynia, slowing of fine finger movements

## Included diagnostic criteria for non delphi conditions:

### Cervical Spondylosis

1. Pain located in head and neck region
2. "3" Q1a – f with cut off points \*
  - < 80° rotation
  - < 60° flexion
  - < 75° extension
  - < 45° lateral flexion \*

- The cut off points for restricted neck movement are taken from: American Medical Association: Guides to the Evaluation of Permanent Impairment (3<sup>rd</sup> edition). American Medical Association, Chicago, 1988

### Cervical Radiculopathy

1. Pain in distribution of a spinal nerve root *and/ or* pain in the cervical spine *with* neurological changes in a spinal nerve root distribution
- 2. "3" Q1g-h



**Acromial Clavicular  
Joint Dysfunction:**

1. Pain over the acromial clavicular joint
- 2 "3" to *Q2k-l*
3. Pain on palpation of the acromial clavicular joint

**Thoracic Outlet syndrome:** 1. Neurogenic symptoms attributable to the lower trunk of the brachial plexus  
2. Signs of reduced blood flow  
3. Positive response to modified Roos Test  
with "1" to *Q11a-b*

**Sub-acromial bursitis:**

1. Pain over the superior/anterior shoulder region
2. Pain on weight bearing through the arm
3. Pain on palpation of the bursa
4. "3" to *Q2c-d*

**Statement regarding multiple authorship**

The results of the MRI study have been published: Greening J, Smart S, Leary R, Hall-Craggs M, O'Higgins P, Lynn B. Reduced movement of the median nerve in carpal tunnel during wrist flexion in patients with non-specific arm pain. Lancet 1999;354:217-8. I wrote the paper and contributed to the study design, design of the MRI protocols, statistical analysis and interpretation of the data, recruitment and screening of patients and control subjects.

Signed:

J.B. Greening

*I certify that, as stated above, Jane Greening*  
B.Lynn (Research supervisor) *contributed a major part of*  
*the work in the paper given*  
*above.*

*Bruce Lynn*  
