

Review article

Forebrain-mediated sensitization of central pain pathways: ‘non-specific’ pain and a new image for MT

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SUMMARY. Manual therapy (MT-) is moving beyond its empirical origins and into an era of evidence-based practice. Mechanisms for the appearance of clinically observed symptoms and signs are being incorporated into its clinical reasoning process. The recent, but well-documented phenomenon, central sensitization, is recognized as being one such mechanism. Anatomical, physiological, behavioural and clinical evidence demonstrate that, in addition to input from the periphery, central sensitization can be enhanced or maintained by supraspinal processes involving cognitions, attention (‘focussing’) and emotions. These forebrain products may, therefore, make a significant contribution to the symptoms and signs of common musculoskeletal presentations such as ‘non-specific’ back pain and fibromyalgia. The evidence can also be interpreted to provide MT with an acceptable role in the management of these patients. © 2002 Elsevier Science Ltd. All rights reserved.

Individualized treatment driven by mechanistic inferences cannot fail to be safer and more effective than empirically based treatment (Max 2000)

Evidence-based medicine is not ‘cookbook’ medicine ... it requires a bottom-up [rather than a top-down] approach (Sackett 1998)

INTRODUCTION

Orthodox health-care practitioners have a professional obligation to attempt to base the selection and delivery of treatment on the likely cause(s) of clinically observed symptoms and signs, rather than on empirically derived formulae (Max 2000). The tendency to largely replace cookbook recipe dictated trial and error with a more mechanisms informed approach to clinical reasoning and decision making is a relatively recent, but major, advance in MT (Zusman et al. 1989; Hides et al. 1994; Jones 1995; Vicenzino et al. 1996; Gifford & Butler 1997). A potent stimulus for this vital transformation with MT has been the growing global demand for evidence-based practice. This is echoed in recent pleas for clinicians to always align their practice according to the best available evidence (Jull & Moore 2000) and

to endeavour to practice from a science base rather than a fad base (Moore & Jull 2000).

To its credit, MT accepted, and is attempting to meet, the up-front challenge of being judged, and guided clinically, by the results of sound basic sciences and applied research. Increasingly, the clinical decision-making process is being informed by evidence from MT research as well as that from related disciplines. As a result, for one thing, MT is recognizing that symptoms are not necessarily the same as mechanisms. This is in keeping with substantial evidence that for a range of clinical pain presentations the same set of symptoms (and ‘signs’) may be caused by different mechanisms in different patients (Deyo & Phillips 1996; McCormack 1999; Woolf & Mannion 1999; Max 2000; Neerinx et al. 2000). Moreover, even these may change over time (Woolf & Mannion 1999). It is difficult to disagree with Woolf & Mannion (1999, p. 1960) when they state: ‘Without identification of the mechanisms, the optimum treatment strategy for the patient’s pain cannot be selected.’

Currently, in addition to the seemingly pointless suffering that ensues, escalating economic and social costs have rendered the identification of likely mechanisms for chronic, ‘non-specific’ musculoskeletal pain and disability particularly important (Fordyce 1995; Wall 1996; Aronoff 1998; Mandiadakis & Gray 2000; Neerinx et al. 2000). The propensity for pain and disability to persist in the

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absence of obvious ongoing primary peripheral pathology is both baffling and challenging. The following discussion will draw together (neuro) anatomical, physiological, behavioural and clinical evidence for the enhancement and maintenance of clinically observed symptoms and signs by central nervous system mechanisms. Specifically, it will describe how, as is the case with nociceptive input from the periphery, forebrain products such as emotions and cognitions can effectively sensitize spinal cord pain pathway neurons – the phenomenon of central sensitization. As a result, sustained, peripherally expressed symptoms and signs, potentially reinforced by secondary consequences of chronic activity-avoidant ‘deconditioning’, are proposed to be largely the result of forebrain-mediated central sensitization.

In this regard, it is important to appreciate that simply because the primary site of pain production is proposed to shift from the periphery to the central nervous system, does not mean there is no longer an acceptable biological mechanism. Nor does the fact that the relevant physiology is predominantly a consequence of supraspinal (forebrain) activity makes this any the less ‘real’ or organic.

The evidence will then be interpreted to create a new image for MT, namely that of informed ‘desensitizer’ of this system. The process of physical and psychological desensitization is proposed to involve a combination of mechanical stimulation (movement-based therapy), accurate information, reassurance and instruction. It is anticipated that this evidence-based image of MT would be readily recognizable and acceptable to all of the major ‘stakeholders’.

THE PRODUCTION OF PAIN

Central sensitization

There is now considerable evidence that, as well as producing changes at their peripheral terminals, more than transient stimulation of unmyelinated C-fibre (Group IV) and thinly myelinated A δ (Group III) primary afferents results in lasting increases in the excitability and responsiveness of neurons in spinal cord pain pathways – the phenomenon of central sensitization (Woolf & Salter 2000).

The key to understanding the relevance of central sensitization to the production, and interpretation, of clinically observed symptoms and signs is to appreciate that spinal cord pain pathway neurons make more than routinely functional hard-wired connections with their prescribed receptive fields. They also have a vast number of redundant ‘subliminal’ connections with surrounding areas and structures. Under normal circumstances, the redundant inputs

are too weak to be effective. Hence, normally the appropriate somatotopic map and sensory specificity are maintained. However, should their usually high thresholds for excitation be significantly lowered for any reason, the potential exists for the anatomy to ‘change’. Under these circumstances, central pain pathway neurons display increased discharges to their normally effective inputs. Importantly, they also begin to respond to near and distant inputs that were formally subliminal, normally inappropriate (e.g. along A β afferents) and non-somatotopic (Woolf & Doubell 1994).

This is the situation that prevails to varying degrees soon after dorsal horn pain pathway neurons receive a suitable barrage of input along unmyelinated and thinly myelinated peripheral nociceptive afferents (Woolf & Doubell 1994). As a result, in addition to the production of excessive pain from local pathological tissue (primary hyperalgesia), clinical manifestations of such anatomical and physiological ‘changes’ include widespread spontaneously arising or non-noxiously provoked pain in distant normal tissue and structures — mechanical allodynia; referred pains; referred tenderness. Space constraints prohibit in depth discussion of the sequence of events and molecular mechanisms responsible for this routine change in the sensitivity and excitability of dorsal horn pain pathway neurons. For these and their clinical consequences, including likely explanations for such esoteric MT concepts such as ‘irritability’ and ‘latent’ or flare-up pain, the interested reader is referred to Woolf & Costigan (1999), Costigan & Woolf (2000), Woolf & Salter (2000).

However, it is of particular relevance to the present discussion that the equivalent of this situation (central sensitization) can also be brought about by activity of pain modulatory systems that descend to the dorsal horn of the spinal cord from the brain. Moreover, that these descending brainstem pain inhibitory and facilitatory systems are heavily connected with, and strongly influenced by activity in, identified forebrain structures. This includes such well-known pain enhancement and maintenance (psychosocial) factors such as cognitions, emotions, selective attention and pain behaviours (Dubner & Ren 1999; Price 2000; Ren et al. 2000). Together, the relevance this might have to enhanced, maintained and disabling non-specific musculoskeletal pain is summarized by Dubner & Ren (1999 p S51):

An imbalance of descending modulatory systems in which there is an increase in endogenous facilitation could lead to innocuous input being perceived as painful. For patients suffering from temporomandibular disorders, fibromyalgia, or low back pain, the diffuse nature and amplification of persistent pain may be in part the result of such an imbalance.

If this is so, in keeping with its aim an attempt to classify patients according to whether they are or are

not likely to respond to appropriate MT interventions (Jull & Moore 2000), such a possibility is of undeniable interest to modern scientific MT.

ENDOGENOUS PAIN MODULATORY SYSTEMS

Loss of inhibitions

The presence of several pain inhibitory and facilitatory centres or nuclei in the mammalian brainstem is now well recognized (Basbaum & Fields 1984; Dubner & Ren 1999). Evidence for their preferred pathway(s) in the spinal cord and their clearly *bipolar* influence on dorsal horn neurons, nociceptive as well as non-nociceptive, has also been forthcoming (McMahon & Wall 1988; Apkarian et al. 1994; Urban & Gebhardt 1999). On balance, the net effect of these descending brainstem systems on spinal cord neurons, normally as well as under routine inflammatory conditions, seems to be inhibitory. However, as will be seen, it is possible for various factors to shift the balance in favour of facilitation. One factor evidently capable of doing so – namely, selective attention – will be addressed further on in the discussion.

Experimental evidence for the existence of descending inhibitory pathways, and their connection with central sensitization, include the observation that bilateral lesions of the dorsolateral funiculus in the rat led to a significant decrease in the latency for paw withdrawal to noxious stimulus (Wei et al. 1999). Dorsolateral funiculus appear to be a preferred pathway for descending pain inhibitory systems (Dubner & Ren 1999; Urban & Gebhardt 1999). Similarly, temporary spinal cord block (lidocaine) caused dorsal horn nociceptive specific and wide dynamic range neurons to expand their receptive fields and increase their responsiveness to afferent input. These effects were further enhanced with experimentally ‘inflamed’ animals (hindpaw injection of complete Freund’s adjuvant or carrageenan) (Ren & Dubner 1996). Supraspinally, anaesthetization (lidocaine) of the nucleus raphe magnus (NRM), a component of the RVM, caused nociceptive-specific neurons in the spinal cord to increase their background discharge, expand their receptive fields and respond in an exaggerated and abnormal manner to subsequent peripheral stimuli (Ren & Dubner 1996). In addition, selective chemical lesion of NRM 5HT-containing (inhibitory) neurons in experimentally ‘inflamed’ animals resulted in demonstrable behavioural ‘pain’ hypersensitivity. This was accompanied by the appearance of the Fos protein bilaterally and in all laminae of the animals’ spinal cord (Wei et al. 1998, 1999). The Fos protein is a gene transcription byproduct and recognized biological marker for

enhanced neural activity (Menetrey et al. 1989). Similar effects were observed in superficial laminae following lesions of an inhibitory noradrenergic locus coeruleus-dorsal horn pathway. Hence, though necessarily limited, the foregoing provides evidence for the existence of brainstem descending inhibitory systems, their general location, preferred pathway and main neurotransmitters, which together are capable of regulating the excitability of spinal cord pain pathway neurons (Wei et al. 1998). Moreover, that disruption of one or more of the elements of this system can result in, among other things, the equivalent of central sensitization.

It should be noted that the net effect of all descending inhibitory systems may not always end up being pain inhibition. Indeed, there is evidence that, at least initially, one function of descending (as well as segmental) inhibitory mechanisms is to ‘focus’ the excitation of dorsal horn pain pathway neurons. The effect is to generate a more urgent, localized and rapid pain signal by suppressing surrounding extraneous neuronal activity (Woolf & Salter 2000). This, of course, is the role attributed to the descending inhibitory function of the so-called diffuse noxious inhibitory controls (DNIC) phenomenon (LeBars & Villaneuva 1988; LeBars et al. 1992). According to this model, descending inhibitory pathways effectively enhance the biologically valuable pain signal by reducing the level of irrelevant ‘noise’ in the system. As Lima (1996) correctly points out, in this way the inhibitory component of the DNIC mechanism is converted into a supraspinally mediated pain *facilitatory* system. Nor is it the only one so far identified. There is mounting evidence for specific brainstem pain facilitatory systems and their controlling influences, both of which are of considerable potential clinical significance (Dubner & Ren 1999; Ren et al. 2000).

Facilitation

Among brainstem nuclei so far identified as the origin of descending (or locally acting) pain pathway facilitatory systems is the nucleus reticularis gigantocellularis (NGC). Low-intensity stimulation in the RVM at or near the NGC has been shown to cause lingering excitation of some spinal cord spinothalamic tract neurons as well as a decrease in the latency of the tail-flick response (Haber et al. 1980; Zhuo & Gebhart 1990). Stimulation of the NGC also enhanced the responses of primate spinothalamic tract neurons to transient noxious stimuli (Haber et al. 1980). Selective lesions (ibotenic acid) of NGC in the ‘inflamed’ rat led to a significant increase in the latency for the paw withdrawal reflex and a marked reduction in the presence of Fos protein bilaterally in all laminae of the spinal cord. Such experiments provide evidence that NGC is capable of enhancing

and/or maintaining central sensitization at the spinal cord level (Dubner & Ren 1999). Significantly, secondary hyperalgesia (referred pain/tenderness), a central sensitization symptom was completely blocked by ibotenic acid lesions of the medulla that included NGC (Urban et al. 1996, 1999).

Recently, Almeida et al. (1999) confirmed the presence of a nociceptively driven pathway from the dorsal reticular nucleus (DRt) of the medulla to superficial (and deeper) laminae of the dorsal horn of the spinal cord. Again, clinically relevant evidence was in the form of spontaneous and provoked behavioural responses in the rat following ipsilateral and contralateral chemical lesions of the DRt. Importantly, the findings were backed up by calculating the number of cells expressing noxiously induced *c-fos* protein in both superficial and deeper laminae of the spinal cord. The Fos protein is known to be a reliable marker of neuronal (hyper)activity (Menetrey et al. 1989). Because it has every appearance of being reverberatory or self-sustaining, the DRt-dorsal horn circuit could be particularly significant clinically, not only with respect to pain amplification but also in terms of chronicity. The authors' concluding theme, while obvious, is one frequently repeated in this literature and worthy of mention at this point. Namely, control of the *balance* between endogenous inhibitory and facilitatory influences on spinal cord pain pathway neurons is an important determinant of clinically observed symptoms and signs.

Identification of nociceptively sensitive 'off' (inhibition) and 'on' (facilitation) neurons in the RVM permits further insight into the bidirectional nature of brainstem descending modulation of spinal cord pain pathway neurons (Fields et al. 1988; Fields 1992). Both types of neuron descend to appropriate laminae (I, II, V) of the dorsal horn of the spinal cord and both may be influenced by stimulation of the PAG. Interestingly, Wei et al. (1999) recently demonstrated that the function of inhibitory 'off' cells may be suppressed (via inhibitory interneurons) by activity in nearby NGC neurons. Thus, NGC neurons probably exert their dorsal horn effects through several circuits. However, one mechanism for endogenous descending facilitation, or sensitization, of spinal cord pain pathway neurons could be the local inhibition of a brainstem descending inhibitory system. Since the net effect of stimulation of NGC is facilitation of central sensitization at the spinal cord level (Ren et al. 2000), it would be of considerable clinical interest to identify anatomical connections, including those from the forebrain, likely to be of influence on brainstem structures such as this.

There is now substantial evidence for pathways from acknowledged rostral 'pain'-relevant cortical and subcortical centres to both the PAG and RVM. There is also compelling behavioural evidence that

these forebrain centres are capable of exerting powerful clinically significant influences on various nuclei located within brainstem structures, including NGC. Together this anatomical, physiological and behavioural evidence helps confirm the long recognized, critical influence that forebrain products such as cognitions, emotions, attention and motivation have on the clinical pain experience. As will be discussed, the evidence further endorses detrimental effects recognized as psychosocial factors have on motor control and adaptive function, both spontaneously and as a result of pain.

FOREBRAIN-MEDIATED CENTRAL SENSITIZATION

Anatomically, dense connections have been demonstrated between relevant forebrain structures and the RVM, both directly as well as via the PAG. These structures include the anterior cingulate (ACC) and insular (IC) cortices and certain subcortical amygdala and hypothalamic nuclei. Brainstem input from the ACC is particularly significant since the ACC has been invested with a pivotal role in integrating sensory and affective with attentional, cognitive and emotional aspects of pain (Rainville et al. 1997; Casey 1999; Hutchison et al. 1999; Davis et al., 2000; Kwan et al. 2000; Price 2000). Along with other techniques and studies, this central role for the ACC has been demonstrated by using positron emission tomography (PET). This technique is able to image changes in cerebral regional blood flow (rCBF) in response to a variety of noxious peripheral stimuli in awake human subjects (Casey 1999). Increases in rCBF responses during noxious stimulation are considered to reflect physiological changes in neuronal activity related to both nociceptive processing and the perception of pain. It is significant that, when methodological and analytical variations are taken into account, the same anatomical regions have been repeatedly highlighted across studies (Bushnell et al. 1999; Casey 1999). Furthermore, the degree of rCBF response was found to correlate with reports of pain intensity in humans (Casey 1999; Hofbauer et al. 2001).

It is of interest to MT that together with the ACC and insular cortices, the most consistently activated supraspinal regions using a variety of noxious stimuli, were *motor* centres, namely, the premotor cortex and cerebellar vermis (Casey 1999). Evidence suggests that complimentary activation of cortical and subcortical motor areas is related to instructions for movements or postures intended to escape painful stimulation (Hsieh et al, 1994; Price 2000). Converging on the ACC is information from higher centres of central processing (S1, S2 via 'corticolimbic' posterior parietal and insular cortices) that is considered to provide the organism with 'an overall

sense of intrusion and threat to physical body and self' (Price 2000). This information is integrated with that from (pre)frontal cortical areas concerned with future implications of the pain and with establishing response priorities. These include decisions and strategies to escape the pain and any pain-evoking situations. Movement and postural 'planning' concerned with the avoidance of pain obviously require intimate anatomical cooperation with (pre and supplementary) motor centres as well as close connections with centres of emotion and motivation (Price 2000).

Behavioural studies incorporating electrophysiologically correlated data with a delayed-response task paradigm have been particularly enlightening. In one such series, primates were rewarded for responding to a randomly delivered transient tissue threatening (but not damaging) peripheral stimulus. It was found that expansion of receptive fields and increased responsiveness (i.e. sensitization) of second-order trigeminal pain pathway neurons were directly related to the strength of engineered *attention* (Dubner & Ren 1999). The evidence suggests that selective attention to relevant stimuli – 'focusing' – activated descending pain modulatory systems, turning the balance in favour of facilitation. The dominance of descending facilitation then led to sensitization of second-order (trigeminal/spinal cord) neurons.

As discussed above, descending modulatory systems originate from and involve multiple sites in the cerebral cortex and brainstem nuclei. Notably, one of these sites, the ACC, has recently been shown to have a prominent role in the encoding of pain, and pain affect, in humans. Moreover, its neurons are known to be highly sensitive to the cognitive state of selective attention (Rainville et al. 1997; Hutchison et al. 1999; Davis et al. 2000). The influence attention ('focussing') can have on the perception of pain in humans recently received endorsement from Miron et al. (1989). This research showed that, with contrived changes in directed attention, human volunteers reported alterations in both the perceived intensity and unpleasantness, hence tolerance, of a transiently painful but non-tissue-damaging thermal stimulus. These and other findings prompted Dubner & Ren (1999) to contend that the addition of behavioural ('forebrain') variable such as *attention* to a potentially *threatening* stimulus results in sensitization of dorsal horn spinal cord neurons. Moreover, that behavioural modulation associated with selective attention to a perceived threat (transient noxious stimulus) utilizes the same forebrain and brainstem structures and mechanisms as are involved in the development, amplification and maintenance of persistent pain following actual tissue damage and inflammation (Dubner & Ren 1999). The critical implication is that because there is a shared central pain producing/sustaining mechanism, the clinical consequences are

likely to be functionally indistinguishable from that initially triggered by the primary (self-limiting) peripheral pathology (Dubner & Ren 1999; Moog et al. 2002).

In any event, the proposal is that by shifting the balance in favour of facilitation, forebrain products such as attention and threat (actual or perceived) would have a role in the magnification, and maintenance, of clinically observed symptoms and signs. This would obviously be of relevance to an evidence-based clinical decision-making process with MT. Relevance begins with recognition of the model. It extends to the attempted identification of patients where, irrespective of 'biomedical' findings, forebrain-mediated central sensitization is strongly suspected of being the cause, or major component, of their prolonged pain and functional disability. Deciding whether individual patients with such pain-perpetuating mechanisms are potential 'responders' or 'non-responders' to some or other MT intervention — and why — is a further issue of relevance.

Responders and non-responders

The sequence of apprehension, uncertainty and gloom is a natural and biologically relevant accompaniment of (survival-threatening) damage to structure (Melzack & Wall 1991; Wall 1979). Hence, an appropriate degree — and duration — of cognitive and emotional 'turmoil' may compound the pain experience. However, certain cognitive styles and personality traits have also been associated with gross amplification of pain and its extension in the absence, or beyond the period for healing, of tissue damage (Waddell et al. 1993; Bacon et al. 1994; Jensen et al. 1994; Barsky & Boris 1995; Gatchell et al. 1995; Woltersdorf 1995; Aronoff 1998; Crombez et al. 1999a; Vlaeyen & Crombez 1999; Bass 2000; Linton et al. 2000; Turner et al. 2000; Vlaeyen & Linton 2000; Ferrari & Schrader 2001; Keogh et al. 2001). These include somatization, catastrophizing and hypervigilance.

Somatization has been defined as '... the propensity to experience and report somatic symptoms that have no pathophysiological explanation, to misattribute them to disease, and to seek medical attention for them (Barsky & Borus 1995, p. 1931). While there appears to be a range of professed 'problem' and severity (Katon et al, 1991; Bacon et al. 1994), the most common complaint is that of pain (Lipowski 1986). It is highly unlikely that somatizers complaining of pain and disability will respond to MT in any cost-effective or sustained way (Lipowski 1986; Woltersdorf 1995). Hence, it would be important to exclude such individuals from among the reportedly large percentage of patients deemed 'problematic' or 'recalcitrant' (Sweet & Reynolds 1992). Given other

health-care priorities, the expenditure of inappropriate resources for this category of patient has been roundly condemned (Kroenke & Mangelsdorff 1989; Deyo 1993; Barsky & Borous 1995; Woltersdorf 1995; Bass 2000; Katon & Walker 1998; Waddell 1996).

Catastrophizing is described as '... expecting or worrying about major negative consequences from a situation, even one of minor importance' (Turner et al. 2000, p 116). It seems reasonable to suspect that this compulsion would be compounded by either a dearth of (or refusal to acknowledge) accurate information, or by threatening misinformation. Such would also appear to be the case with hypervigilance. Hypervigilance is broadly defined as '... a readiness to select out, and respond to, a certain kind of weak or infrequent stimulus [coming] from the internal or external environment' (Peters et al. 2000, p 284). In the present context this means a preoccupation with pain, present or anticipated, and its aura of threat. Thus, there is heightened attention and sensitivity to somatosensory stimuli (bodily signals) perceived to be painful (Aronoff 1998; Crombez et al. 1999a, Ferrari & Schrader 2001; Keogh et al. 2001). Clinically, this is likely to manifest as selective attentional bias for 'pain'; difficulty in shifting attention away from pain-related stimuli; fear of the presence, meaning and consequences of pain; dread, hence avoidance, of actual or anticipated movement-related pain (Waddell et al. 1993; Crombez et al. 1999a; Vlaeyen & Linton 2000; Keogh et al. 2001).

With proper insight, it may be possible to 'change' the thought processes and behaviour of individuals belonging to the latter two categories. The three-pronged approach advocated by Vlaeyen & Crombez (1999) — enquire, explain, expose — would appear to be both applicable and advantageous to MT. The first component, enquiry, is recognized as being an essential preliminary to the clinical management of this type of patient (Woltersdorf 1995; Vlaeyen & Crombez 1999; Bass 2000). Understanding patients' views by defining their beliefs and expectations facilitates delivery of the second component (Bass 2000; May et al. 2000). This is the provision of a rational explanation for their symptoms and its optimum management (Bass 2000; Champion 2000; Gracely 2000). The recommendation is for routine delivery, at the *earliest* opportunity, of accurate information concerning symptom mechanisms and likely prognosis (Linton 1996; Champion 2000). Together with disabuse of potentially disabling notions and fears (e.g. of physical activity), this is predicted to both decrease demands for health care and reduce the number of 'recalcitrant' patients with chronic problems (Linton 1996; Vlaeyen & Crombez 1999; Bass 2000). The recent study by Buchbinder et al. (2001) provides convincing evidence for the economic, and presumably social, benefits of sound

information and advice regarding the cause, prognosis and optimal management of most back pain. In this context, it is worth noting that physiotherapists were recently nominated as ideally 'positioned' (widely consulted, informed, potentially cost effective) to provide accurate information and reassurance to patients with common back pain (Abenhaim et al. 2000). This echoes earlier exhortations (Zusman 1984; 1997), and is currently part of a proposed world-wide campaign to preempt psychosocially and iatrogenically induced chronicity in patients with generally benign and self-limiting musculoskeletal pain (Deyo & Diehl 1986; Allan & Waddell 1989; Fordyce 1995; Hadler 1995; Loeser & Sullivan 1995; Waddell 1996; Aronoff 1998; Burton & Waddell 1998; Nachemson 1999; Abenhaim et al. 2000; Carter & Birrell 2000).

The third component of this proposed physical and psychological 'desensitization' role for MT, that of gradual exposure (in this case to mechanical stimuli), in effect describes the process of clinical MT. Overcoming/preventing 'movement phobia' (Stanton-Hicks et al. 1998) with progressive physical desensitization (graduated passive/active movements) may be in part the result of stimulus-induced pain inhibition. Pain inhibitory systems aroused to effective levels by therapeutic mechanical stimuli might utilize a variety of segmental and descending mechanisms and pathways (Melzack & Wall 1965; Basbaum & Fields 1984; Zusman et al. 1989; Bowsher 1992; LeBars et al. 1992; Vicenzino et al. 1996; Wall 1996; Yarnitsky et al. 1997; Sandkuhler 2000; Sluka & Wright 2001; Maliszka et al. 2002). In addition, although speculative at this stage, reduction in pain with progressively intense passive/active movement is also likely to have a profound cognitive and behavioural impact. Positive reinforcement might come from such recognized entities such as (improved) self-efficacy beliefs, cognitive dissonance and perceived locus of control (Sternbach 1989; Wall & Jones 1991; Vlaeyen & Linton 2000; Asghari & Nicholas 2001). In terms of the original model, movement-generated pain inhibition together with adaptive transformations of formerly 'sensitizing' cognitions, emotions, attention and behaviours, could serve to shift the balance in favour of (descending) inhibition of central pain pathways. If so, 'forebrain-mediated' central sensitization would thereby be steadily overridden, resulting in the restoration of normal sensory processing and stimulus reinterpretation (Melzack & Wall 1991; Stanton-Hicks et al. 1998; Dubner & Ren 1999).

As decreed earlier, any validity of the 'desensitization' hypothesis for MT might have come only through sound research. Physiotherapy and other protocols exist for measuring pain perception and MT-induced pain inhibition (e.g. Zusman et al. 1989; Jensen & Karoly 1992; Vicenzino et al. 1996;

Sluka & Wright 2001; Malisza et al. 2002). Specific questionnaires are available to detect and measure any changes in the appropriate psychological variables (e.g. Rosenstiel & Keefe 1983; Waddell et al. 1993; Jensen et al. 1994; Sullivan et al. 1995; McNeil & Rainwater 1998).

In conclusion, several factors are known or thought to be implicated in the maintenance of the so-called 'non-specific' musculoskeletal pain (and resultant disability). The foregoing evidence-based model is offered on the assumption that increased awareness of likely mechanisms would facilitate accurate categorization of individuals with this currently costly and contentious clinical and social problem (Dubner & Ren 1999; Max 2000; Neerinx et al. 2000; Moog et al. 2002). Evidence-linked classification leading to cost-effective patient management elevates both personal esteem and professional reputation. Furthermore, familiarity with the contribution of early, excessive and sustained 'forebrain activity' might make to the *development* of chronicity, would inform and motivate the vital preventative role some would confer on the physiotherapy profession. Acquiring a reputation for prevention of chronicity wherever possible would be an advance on simply endeavouring to 'change' secondary physical consequences of chronic 'nonspecific' musculoskeletal pain, which, in any event, is no guarantee of successful rehabilitation (Edwards et al. 1992). Such a reputation is sure to be well received in this the Bone and Joint Decade with its major sponsors (WHO, UN) pledging to '... raise awareness of the growing burden of musculoskeletal disorders on society' and promote research into their cost-effective prevention and management (Harris 2001, p 1969).

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