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Understanding Pain in Order to Treat Patients in Pain

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Pain is not the only reason people seek the care of musculoskeletal practitioners, but it is clearly one of the most common symptoms patients report. Pain-associated musculoskeletal conditions are the leading cause of global disability and, despite advances in knowledge and an exponential increase in healthcare costs, the problem only appears to be worsening (Vos et al., 2012). Given the prevalence of pain in the community, it is remarkable that pain is rarely the focus of medical and allied health graduate programs (Briggs et al., 2011, 2013; Jones and Hush, 2011).

Understanding pain, and the factors that contribute to it, is an important first step toward effectively treating and managing patients with pain. Knowledge of pain theory and biology enables clinicians to better understand and explain the full spectrum of pain presentations they encounter, from simple to complex (Moseley, 2003). It affords them an ability to reason through the potential contributors to a patient's pain, informing hypotheses regarding diagnosis, management and prognosis (see Chapter 1 for a full discussion of the hypothesis category clinical reasoning framework) (Jones et al., 2002). Importantly, an understanding of pain ensures all of the hypothesized contributors to pain are appropriately managed or addressed.

In this chapter, we review the complexity of pain from a theoretical perspective and briefly describe the biological and pathobiological processes associated with it. We introduce pain type as an important hypothesis category and attempt to link the clinical signs and symptoms observed in patients with pain to the mechanisms that may underpin them. In conclusion, we consider how reasoning about the contributors to pain can potentially improve patient outcomes.

Understanding Pain

With rare exception, we have all experienced pain, and these experiences influence our understanding of pain. That a small scratch generally hurts less than a deep graze and that pain seemingly lessens as an injury heals imply that the degree of pain we feel relates directly to the extent of an injury. Pain is thus usually interpreted as a symptom indicative of damage to the body. If pain persists, the intuitive explanation is that the injury or disease process that initiated it has failed to resolve.

Unfortunately, the training many clinicians receive reinforces intuitive understandings of pain. Pathoanatomical models of pain that depict pain as a marker of tissue damage remain influential. Most undergraduate textbooks inadvertently portray pain as an inevitable consequence of the activation of a specialized three-neurone 'pain pathway' – pain is considered a symptom of pathology that resolves only after an injury has healed (Martini, 2006; Snell, 2010). Rarely is it acknowledged that such depictions are not fact but trivializations that reflect the ideas of antiquated pain theories that do not stand up to scrutiny (Gatchel et al., 2007; Moayedi and Davis, 2013).

Misunderstandings regarding pain are unhelpful for patients and clinicians alike. Patients who view pain as a marker of the state of the tissues may be reluctant to participate in treatment and activities of daily life (George et al., 2006; Pincus et al., 2002). In acute pain presentations, these patients may rely on passive treatment strategies alone and not see a need to address predisposing and contributing factors that are relevant to both

immediate outcome and minimization of recurrence. In persistent pain presentations, these patients may adopt maladaptive pain-escape coping strategies such as rest or altering the way they move or position themselves in an attempt to protect the painful body part (Darlow et al., 2015; Waddell, 1998) (see Chapter 3 for further discussion of stress and coping theory). They may seek passive treatment strategies that provide only temporary relief, perhaps trying one therapy after another in the search for relief or an explanation for their pain that makes sense (Watson, 2013). Clinicians who view pain as a symptom of pathology will approach the management of people in pain from a purely biomedical perspective – one that focuses solely on the tissues. They may misinform patients about the meaning and source of their symptoms or unintentionally reinforce negative attitudes toward pain in their patients (Bishop et al., 2008; Coudeyre et al., 2006; Darlow et al., 2013). In cases of persistent pain, some clinicians might rely only on passive treatments that offer temporary pain relief but do not address contributing factors. Failure to understand the biopsychosocial nature of all pain may result in some clinicians stigmatizing patients with persistent pain, who do not respond to treatment based on a biomedical model, as having 'psychogenic pain' or being malingerers – adding to the suffering of these patients rather than relieving it (Synnott et al., 2015).

There are compelling arguments as to why solely tissue-based understandings of pain must be rejected. Stories abound of people who sustained serious injuries but felt no pain – for example, soldiers who report horrific yet painless injuries in the midst of battle, shark-attack victims who report painless amputations and sportspeople who play on through injury without pain (Butler and Moseley, 2013; Melzack and Wall, 1996). Everyday experiences such as those scratches or bruises we notice on our bodies but are unable to recall when they occurred attest to this too. Such examples demonstrate that injury, and the sensory information it generates, can occur independent of pain. Conversely, the accounts of phantom limb pain highlight that pain can be felt in the clear absence of pathology and sensory information (Melzack, 1999; Ramachandran and Blakeslee, 1999).

The relationship between pain and pathology is also unclear. One in two people with moderate to severe radiographic osteoarthritic changes in their knees is asymptomatic, whereas 1 in 10 people with severe knee pain will have no evidence of radiographic arthritis (Bedson and Croft, 2008). A similar discordance is noted in spinal pain, where imaging findings of degeneration are highly prevalent in asymptomatic people and appear to be a normal part of aging (Brinjikji et al., 2015). The same holds true for neuropathies. In a large-scale study of patients with diabetes, only 60% of those with severe neuropathy reported pain (Abbott et al., 2011). Indeed, it has been stated that no study to date, for any pain-related condition, has demonstrated a direct relationship between pathology and pain (Clauw, 2015). That is, neither the presence or absence of pain nor the intensity of pain can be accurately predicted by the presence or absence of pathology.

Every pain, whether associated with significant injury or a momentary feeling that facilitates protection, is dependent on meaning and context. Experiments that manipulate the meaning of a noxious stimuli or the mood of the participants receiving the stimulus directly influence the intensity of pain (Arntz et al., 1994; Butler and Moseley, 2013; Moseley and Arntz, 2007). Clinically, the severity of pain has been shown to vary depending on the perceived cause. Soldiers injured in battle report less pain and require less analgesia than civilians undergoing procedures of comparable impact (Melzack and Wall, 1996), and mastectomy patients who attribute pain to returning cancer report higher levels of pain than those who do not (Smith et al., 1998). These examples seemingly suggest that the meaning of pain, survival versus a potentially life-changing event in the first instance and expectations of mortality in the second, influence how much pain is experienced. A growing clinical literature demonstrates that both pain intensity and duration are associated with mood factors, catastrophization, fear and poor expectation of recovery (Chapman and Vierck, 2017; Edwards et al., 2016).

Rather than an accurate marker of tissue pathology, pain is an unpleasant feeling (Moseley and Butler, 2017) that has both sensory and emotive aspects that cannot be extricated (Merskey and Bogduk, 1994). Pain is influenced by factors from the biological, psychological and social domains (Gatchel et al., 2007) and urges the protection (whether it is needed or not) of the body part in which it is felt. In the next section, we consider how the brain theoretically determines the need for protection and how it constructs a pain experience.

We also briefly describe some of the key mechanisms that underpin pain, extrapolating from the basic and clinical sciences.

Key Point

Pain is not an accurate marker of the presence or extent of tissue injury. Patients who view it as such may be reluctant to participate in treatment and activities of daily life. Clinicians who view it as such will approach the management of people in pain from a purely biomedical perspective.

The Biology of Pain – A Brief Primer

Pain Is a Feeling

Pain is a feeling – it occurs in consciousness. It is an unpleasant feeling, and it has a location. These characteristics separate it from 'senses', which are engaged whether or not they are felt, and separate it from emotions, which conventionally refer to automatic bodily responses. Pain is perhaps best considered as a protective feeling, alongside other feelings such as hunger, thirst and dyspnoea – all unpleasant and all compelling triggers for whole-organism behaviour. When we consider 'pain-related mechanisms', we must consider mechanisms by which feelings emerge into consciousness – arguably 'the difficult problem' of life science; we must consider the detection of potentially dangerous tissue events; we must consider everything that occurs in between.

Despite a vast amount of thinking, humans have not yet discovered how consciousness emerges. There are metaphorical accounts, and there are frameworks and even guiding principles, but the notion of hardware – neural and immune cells in the brain – producing such things as feelings remains in the 'magic' category and may well remain there for some time to come. Although we do not know *how* feelings emerge, we do have some solid frameworks that can explain much of *when, why and to what extent* they emerge.

Neurotags

Contemporary theory regarding how the brain produces the wide array of outputs it does is captured to some extent by a model of the brain as a massive collection of neuroimmune networks, or representations, that are in a constant state of collaboration and competition. In modern pain parlance, these representations are often referred to as 'neurotags' (Butler and Moseley, 2013). Neurotags can be thought of as the pain-related mechanism most 'proximal' to pain – the last thing that happens. A full account of neurotags is beyond the scope of this chapter – the reader is referred elsewhere for this (see Moseley and Butler [2017]) – but understanding the main principles that govern the operation of neurotags will allow the reader to integrate the diverse range of factors, covered in theory Chapters 3 and 4 and the case study chapters through this book, that need to be considered when one analyzes why someone is hurting.

A neurotag can be labelled according to the output it generates. For example, a neurotag that results in a given movement command can be labelled as the neurotag for that movement command. A neurotag that results in back pain can be labelled 'back pain neurotag'. The likelihood that back pain will occur at any given point in time can be considered according to the influence of the back pain neurotag. Factors that govern the influence of a neurotag include the efficacy of its synaptic (neuro-neural and neuro-immune) connections, the number of cells involved (its 'mass') and the precision of its connection. One can readily see that the longer one has back pain, the more efficacious its connections become ('neuroplasticity') and the greater its influence. Clinically, this would manifest as allodynia (pain due to a stimulus that does not normally provoke pain) and hyperalgesia (increased pain from a stimulus that normally provokes pain).

The truly biopsychosocial nature of pain is also captured by this neurotag model. Each neurotag is under the influence of a potentially infinite number of other neurotags. For example, a noxious event in the back may well lead to activation of a 'back nociception'

neurotag, which is highly influential over the 'back pain' neurotag; if the patient believes he or she has a back that 'goes out', is 'worn' or is 'degenerated', then each of these beliefs will be held by neurotags. Each of these neurotags will exert some influence over the back pain neurotag. The magnitude of that influence will be determined by the synaptic efficacy, mass and precision of those neurotags.

This idea that neurotags compete and collaborate for influence offers sensible explanations for many observations that are not easily explained by previous models. For example, intriguing perceptual experiments such as those showing very cold stimuli feeling hot, and more painful, when they coincide with a red visual cue (Moseley and Arntz, 2007), more expensive wines tasting better (and activating brain reward circuits) and a raft of visual illusions are all consistent with competing influences of neurotags on other neurotags. Consider also that fear tends to trump pain: the fear neurotag and the back pain neurotag *compete* for priority; any cue that suggests the entire organism is in danger and needs to take protective action will increase the probability of activating the fear neurotag; any cue that suggests a particular body part should be protected will increase the probability of activating the pain neurotag. This makes ecological and evolutionary sense: given the option to protect one's life, or protect one's arm, for example, it would seem most beneficial to do the former. The interactions of diverse neurotags and the individual nature of neurotags, corresponding to patients' unique biopsychosocial makeup, highlight the need for explicit and comprehensive assessment of biological, psychological and social factors (see Chapters 3 and 4 for further discussion of psychological and social factors).

Danger Detection Is Important

It is sensible, when thinking about pain-related mechanisms, to have a sound understanding of how danger is detected and transmitted to the brain. This capacity to detect, transmit and represent danger is called nociception. According to what we currently know about brain activity associated with nociception, nociceptive neurotags are large and have high synaptic efficacy, which means they will be highly influential over pain neurotags.

Nociception is well studied. The tissues of the body are by and large very well innervated by free nerve endings. These free nerve endings are primarily small-diameter and thinly myelinated (Aδ) or unmyelinated (C) fibres, although some are wide-diameter myelinated (Aβ) fibres. Free nerve endings vary in many ways. For example, some have a low threshold, some high; some adapt quickly, some slowly; some have small receptive fields, and some have large ones. In a normal physiological state, it is the high-threshold free nerve endings that function most like nociceptors (or 'danger detectors') – they only respond to large and rapid changes in the tissue environment.

Free nerve endings terminate in the spinal cord, where they enter a complex matrix of neurones, interneurons and immune cells. Contemporary neurophysiological models of the grey matter of the spinal cord relate most closely to those of the brain. We can apply the neurotag idea here as well, conceptualizing the spinal cord as a long tube of brain-like neuroimmune networks, or neurotags, surrounded by the white matter 'freeways' via which messages travel quickly and without interruption to and from higher centres (Moseley and Butler, 2017). The output of spinal neurotags will be to either influence other spinal neurotags or activate projection neurones that terminate in the body (these are motor neurones, which emerge from the ventral horn of the spinal cord) or supraspinally (these are spinal nociceptors, which emerge from the dorsal horn and join the ascending 'freeway' to the thalamus). This complex matrix within the spinal cord offers a mechanism by which massive computational capacity can occur at a spinal level. Indeed, contemporary pain theory rejects the idea of the dorsal horn working as a relay station for nociceptive input, endorsing instead the idea of the dorsal horn working as a processing station that determines the spatial and temporal features of any further signals of danger that are transmitted to the brain.

Danger detectors have a wide variety of sensors in their walls – ion channels that respond to chemical, thermal or mechanical changes in the tissues or to a shift in the voltage across the cell membrane (Ringkamp et al., 2013) (for full review in accessible language, see Moseley and Butler [2017]). The response profile of a given danger detector will reflect the mix of ion channels in its membrane – some respond to small and innocuous changes in the

understand the overall experiences of pain and disability, we examine two frameworks important to musculoskeletal clinicians' assessment, reasoning and management: the stress-diathesis model (Shanahan and Macmillan, 2008; Elder, 1994) and the International Classification of Functioning, Disability and Health (ICF) model (World Health Organization [WHO], 2001) framework of health and disablement (Shanahan and Macmillan, 2008; Rowland, 1989). Both models include identifying contributing factors and modifying resources that are available to patients that also influence outcomes.

The stress and coping model (Lazarus and Folkman, 1984b) is used to identify what coping behaviours preserve well-being in patients with musculoskeletal disorders while facing stressful experiences with acute or chronic conditions. Integrating the new lens of health as described by the ICF framework introduced in Chapter 1 requires consideration of the larger personal and environmental influences around the individual. Finally, this chapter explores self-rated health and self-efficacy from the perspective of social cognitive theory (Bandura, 1977b; Bandura, 1977a) and social support as a social resource for health in the stress and coping model (Lazarus and Folkman, 1984a, 1984b). Understanding both individual-level and social-level concepts will serve to broaden the understanding of health behaviours that influence patients with musculoskeletal disorders and ultimately influence treatment and related outcomes in caring for individuals with musculoskeletal disorders.

Behavioural Factors in Musculoskeletal Disorders

Individuals with musculoskeletal disorders often report decreases in physical health (Weinstein et al., 2008; Fritz et al., 1998; Whitman et al., 2003). Decreased physical health, either real or perceived, can impact an individual in many ways. Overall, it is known that those who have decreased physical health reduce or eliminate participation in daily living, physical, social and recreational activities. A lack of activity has been shown to lead to other stressors such as obesity and general physical deterioration that may eventually result in further disability with the onset of cardiovascular and other serious health problems (Pinsky et al., 1990). Activity restrictions may also lead to low self-confidence, fear-avoidance behaviours, depression and other psychological problems that further restrict the person with a musculoskeletal disorder from participation in activities of daily living (ADLs), physical activities, recreational activities, social activities and community functions (Shakil et al., 1999; Kirkaldy-Willis and Bernard, 1999; Hirsch and Liebert, 1998). Chapter 4 further explains how psychological factors such as maladaptive cognitions (e.g. pain and 'illness' representations or beliefs, catastrophizing), distress, fear based beliefs and related avoidance behaviours are negative influences on the stressors of pain and disability and result in declines in treatment success in musculoskeletal disorders in general (Waddell et al., 1993; Flynn et al., 2002; Buer and Linton, 2002). Psychological distress, from frustrations to anxiety and depression, and fear-avoidance behaviours correlate with reduced participation in functional daily tasks, indicating a higher risk for disability. Although diagnosis of depression is beyond the scope of practice of musculoskeletal clinicians, some studies have shown that depressive symptoms and high fear-avoidance scores can improve during some areas of musculoskeletal management and result in positive changes in patient outcomes of pain and disability (Fritz and George, 2002; Brox et al., 2003; Whitman et al., 2006). In addition, research has demonstrated that using an enhanced or multimodal team approach to treatment results in improved patient outcomes for musculoskeletal conditions such as low back pain (Sunderland et al., 1992; Whitman et al., 2006). Even though some physical, cognitive and psychological factors contributing to higher pre-treatment pain and disability and post-treatment outcomes have been identified in many musculoskeletal conditions, identifying all the behavioural factors that influence individuals with musculoskeletal disorders continues to be incomplete.

Similar to other health conditions, the daily lives of individuals with musculoskeletal disorders likely involve unanticipated challenges. Patients with musculoskeletal disorders must learn to navigate life with the stress of either acute or chronic pain, cope with reduced functioning, experience limitations to their physical and social abilities, manage through decreased activities, and face fears about recurrence or worsening of their condition. Previous research on arthritis and other health conditions has identified that persistent psychosocial needs can decrease the effectiveness of medical treatment, general

health status and quality of life while increasing healthcare costs (Sullivan et al., 2005; Brooks, 2002; Steiner et al., 2002). Although unidentified in many areas of musculoskeletal literature, unaddressed personal and social needs may contribute to reduced participation with treatment and follow-up recommendations, diminished self-care and reduced overall health management (Marinelli and Orto, 1999). Therefore, we recommend that clinicians have a good understanding of the patient's experience of stressors, understand coping behaviours and identify patient resources that may contribute to an improved outcome.

Stress and Coping Model

Pain and disability have been identified as primary stressors in previous musculoskeletal literature. Differing experiences with musculoskeletal disorders result in different appraisals of the stressors of pain and disability. Moreover, individuals with musculoskeletal disorders can have different outcomes related to the experience of pain and disability even with the same treatment approaches. To better understand these main stressors, this chapter uses the underlying theoretical concepts in the stress and coping model (Lazarus and Folkman, 1984b) to define both stress and coping as well as identify the relationship of these concepts in musculoskeletal disorders. Within the stress and coping model (Lazarus and Folkman, 1984b), stress involves the relationship between an individual and his or her environment. This relationship or transaction between individuals and their environment indicates that stress is more than an internal stimulation or specific pattern of physiological, behavioural or subjective reactions (see Fig. 3.1). Two key mediators within the person–environment transaction are cognitive appraisal and coping effort. Cognitive appraisals and coping efforts are influenced by moderators such as personal and situational factors that result in individual adaptations that impact health on many levels. An understanding of stress and coping constructs underpins musculoskeletal clinicians' assessment of individual patients' stressors and coping behaviours that then informs how these may be addressed within clinical management.

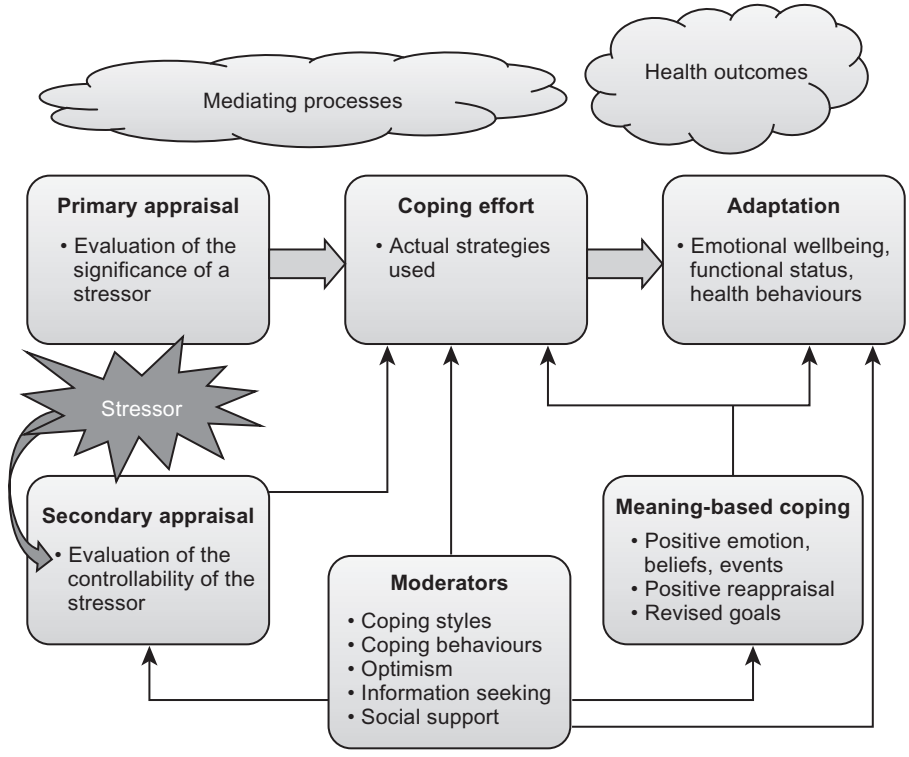

Fig. 3.1 Stress and coping model and stressful health conditions *(Adapted with permission from Glanz et al. [2008].)*

Cognitive Appraisal

The cognitive appraisal or evaluation by the individual is paramount to determining if the stress is threatening to his or her well-being or surpassing his or her resources. Upon appraising a stressor, the theory asserts that people engage in coping, defined as fluctuating behavioural exertions, in an effort to manage that stressor. The cognitive appraisal process helps an individual determine both the controllability and availability of coping resources identified as necessary to manage the stressor(s) (Lazarus and Folkman, 1984b).

Cognitive appraisal is a necessary component of dealing with a stressor. It accounts for the different ways in which individuals react to similar events. Health conditions such as those resulting in pain provocation and disability, as in many musculoskeletal disorders, can cause stress in nearly every person, yet people vary in their reactions and interpretations of the same event and condition (Lazarus and Folkman, 1984b). This variability in cognitive appraisals can change a person's level of vulnerability during a stressful health condition. Vulnerability is closely related to appraisal because vulnerability increases as a person appraises that he or she has reduced coping resources available. Vulnerability reflects the inability of individuals to withstand adverse impacts from a single stressor or multiple stressors to which they are exposed. It can be associated with a pattern of thought that is believed to predispose the individual to psychological problems and feelings of hopelessness. In addition, the variability of individual appraisals, as well as the individual's responses, helps to explain why some individuals experience similar health conditions but have differing quality, intensity and duration of physical, social and emotional outcomes.

Personal and Situational Factors

Two types of factors influence the cognitive appraisal process: personal factors and situational factors (Lazarus and Folkman, 1984a, 1984b). Personal factors consist of the personal values that motivate individuals to make certain decisions and beliefs that give the individual a personal sense of control. Therefore, at the individual level, commitments and beliefs are part of an individual's process of appraisal. Commitments are expressions of what is important to a person and can be related to vulnerability. For example, where a participation restriction may be an inconvenience to one patient that does not unduly add to the patient's stress, for another patient, the value and even self-identity he or she attaches to reduced or lost participation (e.g. work, sport) can represent a significant personal loss associated with increased vulnerability. The deeper a person's commitment, the greater potential for threat, but also the greater the push toward ameliorative action and hope. Beliefs are also important in determining how a person evaluates a stressful event or health condition. Beliefs of personal control over situations can relate to how an individual believes internal self-responses to situations (e.g. emotions) can be controlled. General control beliefs relate to the extent that the person believes the health-related outcomes can be controlled. For example, two patients may experience the same musculoskeletal injury, such as an anterior cruciate ligament rupture of the knee. One patient has had previous experience with an acute injury and rehabilitation and is confident he can emotionally manage this situation. The other patient is going through a difficult divorce and just went through the death of her mother. Her internal self-responses are exaggerated compared with normal and are highly emotional, so she does not believe that she can handle this additional life event. These beliefs will greatly impact each patient's evaluation of the stressful health condition and will ultimately affect the coping responses and strategies that they use to manage their knee rehabilitation. When working with the second patient who has negative health beliefs and a reduced sense of control, the clinician must work to address these beliefs and help improve her sense of control in order to help augment positive coping behaviours.

Another influence to the appraisal process is situational factors, which play a critical role in determining the external controllability of the stressor and what ameliorative action can be taken (Lazarus and Folkman, 1984a, 1984b). Situational factors can include predictability and uncertainty, temporal and life course factors and ambiguity. The modifiability of situational factors will vary, and as such, the potential to influence how and to what extent the stressor can be managed also varies. Although factors such as socio-economic status (SES) – recognized as a strong predictor of poor outcomes across a variety of health

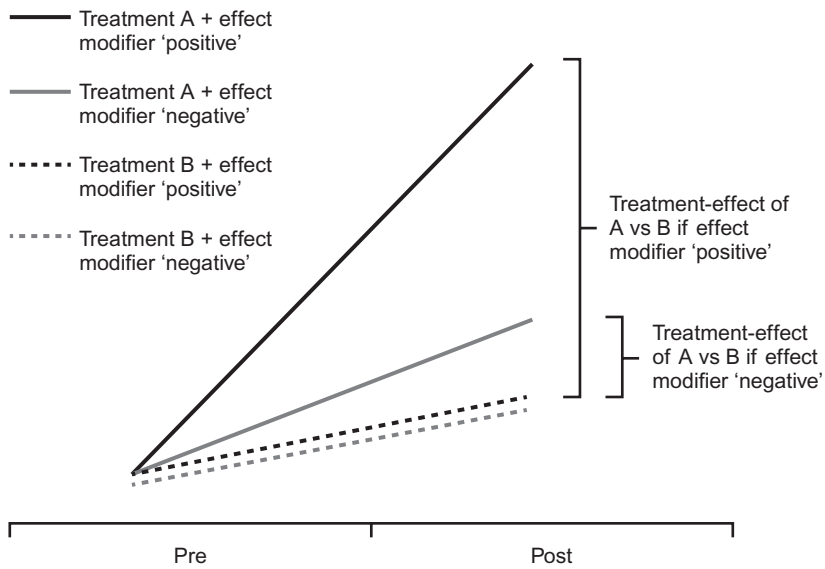

Fig. 5.1 Illustration of a treatment effect that is modified by a patient's status on a baseline variable.

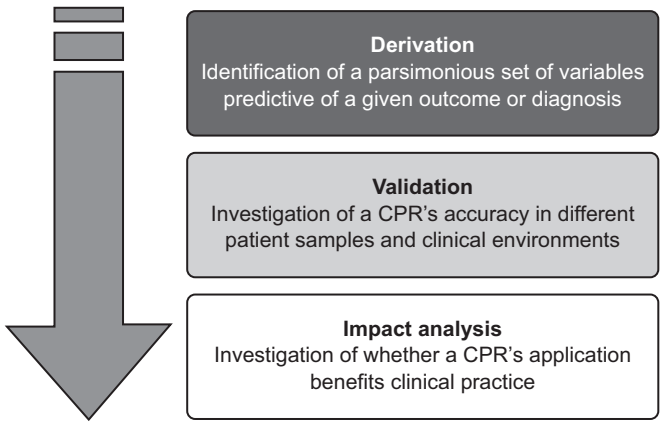

Fig. 5.2 Stages in the development of a clinical prediction rule (CPR) *(Adapted with permission from Childs and Cleland [2006])*.

Derivation

The first step in the development of a CPR is derivation. This process commences with the identification of a meaningful problem for which the development of a CPR may be perceived as clinically useful. Considerations that help inform the need for a CPR include the complexity of clinical decision-making, the accuracy of unassisted clinician judgement, clinician attitudes, variations in practices and the hypothesized potential for a tool to beneficially impact practice by improving patient outcomes or improving resource efficiencies (Fritz, 2009; Stiell and Wells, 1999).

The study design required to derive a CPR is dependent on the type of CPR under development. Diagnostic CPRs are derived in cross-sectional studies, prognostic CPRs are derived in longitudinal cohort studies and prescriptive CPRs require randomized controlled trials (Hancock et al., 2009; Hill and Fritz, 2011). In all instances, a meaningful, valid and clearly defined dependent outcome that is able to be reliably measured requires selection (Stiell and Wells, 1999). A small number of candidate predictor variables also need to be selected *a priori* and considered within the context of their hypothesized predictive performance, validity and reliability, as well as their practicality and availability within the

TABLE 5.2

TECHNIQUES USED TO DEVELOP CLINICAL PREDICTION RULES

Technique	Advantages	Disadvantages
Univariate analysis	Simple to develop. Easy to use.	Predictors may not be independent. Weightings are arbitrary. Less accurate.
Multivariable analysis	Improved accuracy.	Slightly more complicated to develop.
Nomograms	Improved accuracy. Easy to use.	More complicated to develop.
Classification and regression trees (recursive partitioning)	Easy to use. Enables development of rules that are optimized for sensitivity or specificity.	Can often be less accurate than other techniques. Does not work well for continuous variables. Prone to overfitting.
Artificial neural network	Improved accuracy over time with new data. Identifies complex non-linear relationships and interactions.	More complicated to develop. Prone to overfitting. Hard to apply in most clinical settings.

(Adapted from Grobman and Stamilio [2006] and Adams and Leveson [2012])

clinical environment (C. Cook et al., 2010; Lubetzky-Vilnai et al., 2014; Seel et al., 2012). Clinical judgement, literature reviews, focus groups and questionnaires have been used to select candidate predictor variables in some CPR derivation studies (Dionne et al., 2005; Hewitt et al., 2007; Heymans et al., 2007, 2009).

The patient population sampled in CPR derivation studies needs to represent the spectrum of patients to which the tool is likely to be applied (Stiell and Wells, 1999). Generally, large sample sizes are required to satisfy the assumptions of the statistical techniques that are used and to also generate greater precision of the findings (Childs and Cleland, 2006). Larger sample sizes are particularly required when investigating an outcome with a very low prevalence (e.g. cancer in patients with low back pain), when testing large numbers of candidate predictors and when investigating treatment effect modifiers (Babyak, 2004; Brookes et al., 2004).

Once data collection is complete, statistical analysis is used to identify the candidate variables that have a significant predictive relationship with the dependent outcome. There are several different techniques that have been used to derive CPRs in the medical literature. Table 5.2, adapted from Grobman and Stamilio (2006) and Adams and Leveson (2012), provides an overview of these techniques and their relative advantages and disadvantages.

Univariate analysis, whereby the relationships between each predictor variable and the dependent outcome are examined separately, is the simplest technique but has several limitations. Most notably, it does not account for the relationship among candidate predictor variables. Multivariable analysis overcomes this limitation by examining the independent relationship of each predictor variable with the target outcome, and it also enables the assignment of variable weightings based on the interpretation of the regression coefficients (Laupacis et al., 1997). Various forms of multivariable analysis have been commonly used to derive CPRs (Bouwmeester et al., 2012), and in some cases, automated methods of variable selection (e.g. forward stepwise, backward deletion, best subset) are applied. However, given the increased chance of identifying spurious associations using automated procedures, these approaches may not be well suited for CPR development and may best be reserved for exploratory analysis (Babyak, 2004; Katz, 2003). Multivariable models are generally well suited to construct nomograms, which are graphical calculating tools that facilitate the application of otherwise-complicated mathematical equations (Grobman and Stamilio, 2006).

Classification and regression trees are another approach used to derive CPRs. This analysis uses non-parametric statistical procedures to identify mutually exclusive and exhaustive subgroups based on the variables that predict the dependent outcome (Lemon et al., 2003). Recursive partitioning accounts for interactions between predictor variables

(E. F. Cook and Goldman, 1984; Dionne et al., 1997) and is subsequently better suited for deriving CPRs from datasets with interacting variables than logistic regression (Katz, 2006). This approach is also considered to be well suited in instances where a CPR requires optimization of either sensitivity or specificity (Stiell and Wells, 1999).

Artificial neural networks require advanced computational resources and are another approach used to develop CPRs. Artificial neural networks are inherently statistically more flexible than regression approaches and, all else being equal, provide models that better fit the study data (Kattan, 2002). However, as a consequence, they are also more vulnerable to overfitting, thus potentially reducing the likelihood that these approaches will perform well outside of the derivation study data (Tu, 1996).

To illustrate the development of a CPR, the Ottawa Knee Rule (Table 5.1) will be used as an example (Stiell, Greenberg, et al., 1995). A need for a tool to help decide which patients require an x-ray was based on the finding that whilst almost three-quarters of patients presenting with acute knee injury to an emergency department were referred for radiology, only 5% were identified to have a fracture (Stiell, Wells, et al., 1995). This contributes to increased costs of care, increased waiting times and unnecessary radiation exposure. It was also identified that experienced clinicians believed that the probability of a fracture was less than 10% in the majority of patients sent for radiology (Stiell, Wells, et al., 1995).

Consequently, a prospective study was conducted involving 1047 adult patients with acute knee injuries presenting to one of two university hospital emergency departments in Ottawa, Canada. The dependent outcome was any fracture of the knee seen on plain x-ray and was determined blinded to knowledge of the candidate predictor variables. For ethical reasons, patients thought not to require a knee x-ray were not sent for radiology, but follow-up was conducted via a telephone questionnaire with the aim of detecting any missed fractures. Twenty-three candidate predictor variables were selected based on clinician judgement, literature review and pilot study data. Explicit definitions of each variable were provided to clinicians in a handout.

Following data collection, recursive partitioning was used to derive the CPR. The tool was developed to optimize sensitivity, given that a missed fracture would be of greater consequence than an unnecessary x-ray. Many different models were identified to fit the data, and the research team decided to select the model that gave the greatest specificity and used the fewest number of variables whilst maintaining 100% sensitivity. The accuracy of the Ottawa Knee Rule in the derivation study was a sensitivity of 100% (95% confidence interval [CI] 95%–100%) and a specificity of 54% (95% CI 51%–57%).

Validation

A CPR models the study dataset from which it was derived (Beattie and Nelson, 2006). Consequently, it may not always perform well when applied outside of this original context (Justice et al., 1999). Validation is the second stage of a CPR's development and functions to examine the internal validity and generalizability of the derived tool in new patient populations and clinical environments (McGinn et al., 2008). Validation of a CPR is therefore not something achievable within a single study but, rather, an attribute that arises across multiple investigations (Hancock et al., 2009).

Methodological issues within a derivation study that challenge the internal validity of a CPR will have consequences for the tool's ability to perform well in other studies (C. Cook, 2008). However, there are at least three reasons why even a robustly derived CPR may not necessarily perform well outside of the original study (McGinn et al., 2000). These are as follows:

- Chance associations. It is possible that some statistically significant relationships identified in the derivation study are purely due to chance. Consequently, it is unlikely that such associations will hold true in new datasets, thus reducing the predictive performance of a CPR.
- Differences related to the patient population or clinical environment. It is possible that some of the predictive relationships identified in the derivation study are unique to the patient sample or clinician group under investigation. As such, derivation study findings may not generalize to other patient and clinician populations.

- Differences related to the implementation of a CPR. Inconsistencies may arise with regard to the operational definitions of predictor and dependent variables, as well as the accurate application and interpretation of the rule. These will influence a CPR's predictive performance.

Statistical validation (e.g. split samples, bootstrapping) will only account for the first of these threats (McGinn et al., 2000). As such, prospective studies involving different patients, clinicians and clinical settings are required to validate a CPR. 'Narrow validation' refers to the process by which a CPR is tested for its ability to replicate its predictive performance in patients and settings similar to those of the original derivation study (Kamper et al., 2010; Keogh et al., 2014; McGinn et al., 2000). The findings of such studies give insight into the variability of the predictive accuracy of a CPR in a specific patient population (Kent et al., 2010). 'Broad validation', by contrast, examines the generalizability of a CPR to different settings and patient populations unlike those in used in the derivation study (Kamper et al., 2010; Keogh et al., 2014; McGinn et al., 2000).

Toll et al. (2008) further delineate between the temporal, geographic and domain validation of a CPR. Temporal validation refers to the replication of a CPR's performance over time, with little change to the patient population sampled or other elements of the clinical setting. Geographic validation refers to the investigation of a CPR's performance in similar patient populations but in different clinical environments. Finally, domain validation, which is considered to provide the strongest evidence of generalizability, refers to the assessment of a CPR's performance in different clinical environments and in different patient populations that differ non-randomly from that of the derivation sample.

Several studies have contributed to the validation of the Ottawa Knee Rule (Bachmann et al., 2004). Ketelslegers et al. (2002) investigated the performance of this tool when applied by clinicians with differing levels of training in an emergency teaching centre in Brussels, Belgium. Medical students and surgical residents were trained in the accurate implementation of the CPR by the research team. The 261 patients recruited in this study were assessed with regard to their status on the Ottawa Knee Rule. Blinded outcome assessment for the presence of a fracture was determined by x-ray (84%) or by telephone or face-to-face follow-up. The results of this study demonstrated that the Ottawa Knee Rule had a sensitivity of 100% (95% CI 99%–100%) and a specificity of 32% (95% CI 26%–38%). No difference in the predictive accuracy of the CPR was identified between medical students and surgical residents, thus providing evidence of generalizability of the tool to different clinician populations of varying experience. The finding of the 100% sensitivity of the tool is also consistent with that of the derivation study and provides further evidence of the predictive performance of the CPR in identifying patients presenting with acute knee injury who are unlikely to benefit from radiological assessment.

Impact Analysis

The final stage of a CPR's development is called 'impact analysis' and is the investigation of whether a tool's application in clinical practice results in meaningful beneficial consequences, such as improved outcomes or resource efficiencies (Childs and Cleland, 2006). This step is important because even a well-validated CPR may not necessarily outperform unassisted clinician judgement. Further, if a CPR is difficult to use or if there are other factors that impede its implementation, it may not necessarily be successfully adopted in clinical practice (McGinn et al., 2000). Despite the growing volume of CPRs relevant to musculoskeletal practitioners that have been derived at this time, very few have undergone any form of impact analysis (Georgopoulos and Taylor, 2016; Haskins et al., 2015a, 2015b, 2012; Kelly et al., 2017; May and Rosedale, 2009; Stanton et al., 2010; van Oort et al., 2012; Wallace et al., 2016).

The best study design to conduct an impact analysis is a randomized controlled trial, whereby the outcomes produced from the use of a CPR are able to be rigorously evaluated (Toll et al., 2008). Randomization may be at the level of the patient, the clinician or the facility, with the latter helping to minimize potential contamination (Wallace et al., 2011). Before-and-after designs are often a more feasible approach to assessing the impact of the use of a CPR; however, the evidence from such designs is weaker than that produced from

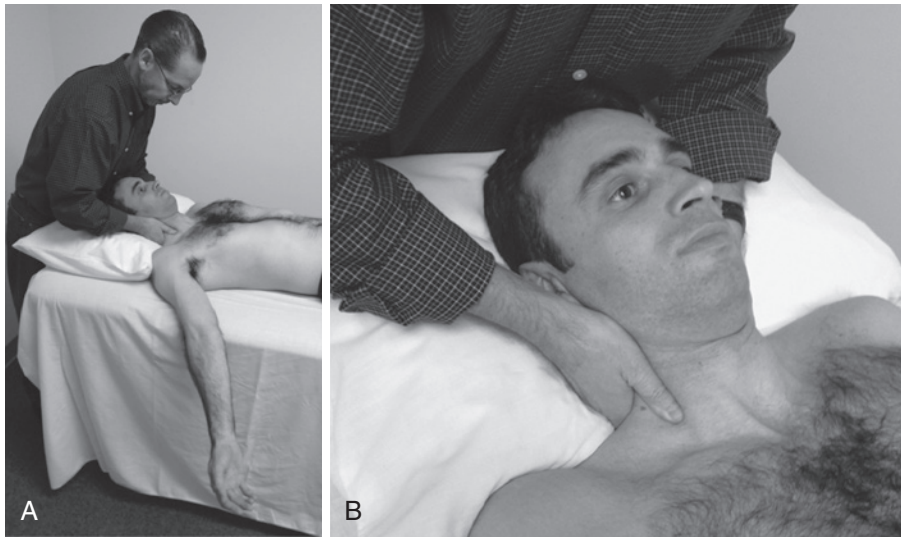

Fig. 7.4 Unilateral anterior-posterior (A-P) pressures at C5–C7 with the upper extremity in shoulder abduction and elbow extension to preload the upper-quarter neural tissues. (A) Patient and therapist positions. (B) Close-up view of the therapist's hand contacts.

and pain. A-P and P-A glides of the radial head were much less stiff. Large-grip pressure was significantly improved and much less painful. $ULNT_{MEDIAN}$ did not provoke lateral elbow pain until 20 degrees from full elbow extension. Henry was instructed to continue performing the active craniocervical flexion exercise but place his arm in 60 degrees of shoulder abduction to preload the upper-quarter neural tissues as during treatment.

Reasoning Question:

6. Please discuss your rationale for the grades of cervical mobilization used (III and IV). Also, what do you hypothesize underlies the treatment responses occurring – for example, how does treating the cervical spine affect radial head glide stiffness/pain and grip strength/pain?

Answer to Reasoning Question:

The perceived restrictions in mobility during the examination using unilateral A-P pressures suggested that stiffness from C5 to C7 contributed to the peripheral sensitisation of lateral elbow and neural structures. Additionally, Henry's symptoms were low on the irritability scale (Maitland, 1991). It was therefore considered appropriate to use grades of mobilization that are thought to be able to address both 'through-range' (Grade III) and 'end-range' (Grade IV) stiffness (Maitland, 1986, 1991). Lastly, Grade III and IV mobilizations might also provide a more appropriate stimulus to elicit the neurophysiological responses described next (Bialosky et al., 2009; Bialosky et al., 2018).

Neurophysiological mechanisms most likely explain why cervical mobilization appeared to make relatively rapid changes in impairments at the elbow. Cervical mobilization provides a mechanical stimulus that activates analgesic responses from higher centres in the central nervous system (e.g. periaqueductal gray area of the midbrain) and spinal cord (Bialosky et al., 2009; Bialosky et al., 2018; Chu et al., 2014; Schmid et al., 2008; Wright, 1995). This type of neurophysiological response to cervical mobilization has been documented in patients who have lateral epicondylalgia (Vicenzino et al., 1998, 1996). The end result clinically is that cervical mobilization can be associated with immediate improvements in passive elbow extension range/pain, radial head glide stiffness/pain, grip strength/pain and neurodynamic testing range/pain. The reduction in signs of sensitivity in lateral elbow and neural structures after cervical mobilization might also allow subsequent treatment directed to the elbow itself to be more effective (Hoogvliet et al., 2013).

Clinical Reasoning Commentary:

As discussed in this answer, the neurophysiological effects of manual therapy are now well documented as the likely mechanism underpinning short-term improvements in musculoskeletal signs and symptoms. Although use of manual therapy has been criticized by some for its lack of efficacy in producing long-term improvements, this fails to appreciate that contemporary musculoskeletal practice generally

promotes selective use of manual therapy as a component of management, whereby short-term improvements in pain and function enable inclusion of additional (or progression of existing) management strategies. Skilled clinical reasoning following a comprehensive examination enables identification of where manual therapy may be adventitious as part of a differential diagnosis and, as discussed in this answer, as a means to decreasing sensitivity that may optimize other management strategies.

TABLE 7.2

PATIENT-SPECIFIC FUNCTIONAL SCALE (PSFS) SCORES AT THE THIRD APPOINTMENT*

Activity	Initial Exam (Day 1)	Appointment 3 (Day 8)
Computer	4	6
Gardening	4	5
Swing golf club	0	1
Average	**2.7**	**4.0**

*Each activity nominated by the patient is rated from 0 (unable to perform the activity) to 10 (able to perform activity at 'pre-injury' level).

Appointment 3, Day 8 (4 Days Later)

Henry reported no problems after the second appointment and no problems with progression of the active craniocervical flexion exercise. He noticed improvements in computer work and power-grip activities as reflected by his PSFS ratings (Table 7.2).

Active and passive extension of the right elbow were limited by stiffness at 10 degrees from full extension (20 degrees from full extension at appointment 2). Passive extension still provoked lateral elbow pain. A-P and P-A glides of the radial head continued to be stiff and painful. Large-grip pressure (elbow extended) continued to improve but still provoked lateral elbow pain. $ULNT_{MEDIAN}$ did not provoke lateral elbow pain until 20 degrees from full elbow extension (30 degrees from full elbow extension at appointment 2). Right unilateral A-P pressures at C5 to C7 were less stiff and did not provoke as much right low cervical discomfort.

Treatment continued with mobilization of right unilateral A-P pressures from C5 to C7 with the arm abducted to preload the neural tissues. Although cervical mobilization continued to reduce end-range pain with elbow extension, improve grip pressure and reduce lateral elbow pain provoked by $ULNT_{MEDIAN}$, it had less impact on stiffness with end-range passive elbow extension and with A-P and P-A glides of the radial head. Treatment was progressed by adding Grade III and IV A-P glides of the radial head with the elbow extended and forearm supinated. Lateral elbow pain was provoked in rhythm with each oscillation. Radial head mobilization decreased end-range stiffness and pain with active and passive elbow extension and further improved grip pressure. However, it did not change $ULNT_{MEDIAN}$. Henry continued the active craniocervical flexion exercise with the arm in abduction and was instructed in self-mobilization of elbow extension in a partial weight-bearing position (Fig. 7.5). Provocation of lateral elbow pain at the end range of the self-mobilization technique was permitted.

Appointment 4, Day 11 (3 Days Later)

Henry reported no problems from adding radial head mobilization and self-mobilization into elbow extension. His bouts of computer work had increased to 30 minutes, and symptoms after power-grip activities were consistently settling in less than 45 minutes. He also reported that his morning stiffness lasted less than 10 minutes with elbow flexion and extension movements.

Treatment continued with right unilateral A-P mobilization of C5–C7 with preloading of the upper-quarter neural tissues (now 90 degrees of shoulder abduction with elbow extended) and A-P glides of the radial head in elbow extension and forearm supination. The active craniocervical flexion exercise was progressed by placing the arm in 90 degrees

Fig. 7.5 Patient position and hand placement to self-mobilize elbow extension in partial weight bearing of the upper extremity. Arrow shows direction of force to self-mobilize elbow extension.

TABLE 7.3

PATIENT-SPECIFIC FUNCTIONAL SCALE (PSFS) SCORES AT THE FIFTH APPOINTMENT*

Activity	Initial Exam (Day 1)	Appointment 5 (Day 15)
Computer	4	7
Gardening	4	6
Swing golf club	0	2
Average	**2.7**	**5.0**

*Each activity nominated by the patient is rated from 0 (unable to perform the activity) to 10 (able to perform activity at 'pre-injury' level).

of shoulder abduction. Henry also continued with self-mobilization of elbow extension in a partial weight-bearing position.

Appointment 5, Day 15 (4 Days Later)

Henry continued to have no problems with treatments or home exercises. PSFS ratings indicated a clinically important improvement in function compared with the initial examination (Abbott and Schmitt, 2014; Hefford et al., 2012) (Table 7.3).

Active and passive extension of the right elbow had improved to 5 degrees from full extension. Passive elbow extension still provoked lateral elbow pain at the end range of movement. Active and passive forearm supination (elbow in 90 degrees flexion) had improved to 75 degrees (85 degrees on left) but still provoked lateral elbow stiffness at end range. A-P and P-A glides of the radial head were much less stiff and less painful. Large-grip pressure (elbow extended) was still reduced, but Henry stated that lateral elbow pain provoked during this test was 50% less intense than at the initial examination. $ULNT_{MEDIAN}$ no longer provoked lateral elbow pain at 20 degrees from full elbow extension. Right unilateral A-P pressures at C5–C7 continued to be less stiff and provoked less discomfort in the right low cervical area.

Improvements in elbow extension and $ULNT_{MEDIAN}$ necessitated progression of the physical examination to continue to identify comparable findings for monitoring Henry's condition (Maitland, 1986, 1991). The passive elbow extension-adduction test (Hyland et al., 1990; Maitland, 1991) was very stiff on the right and provoked more intense lateral elbow pain than passive extension. $ULNT_{RADIAL}$ was rechecked with Henry's improved amount of elbow extension. Passive wrist/finger flexion during the test still provoked lateral elbow and forearm pain. However, in contrast to the initial examination, structural differentiation by decreasing the amount of shoulder girdle depression reduced these symptoms. Resisted

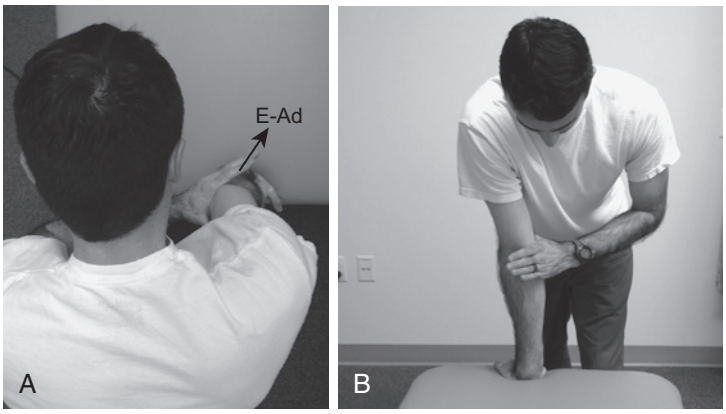

Fig. 7.6 Self-mobilization of elbow extension-adduction in partial weight bearing of the upper extremity. Patient position and hand placement are the same as for self-mobilizing elbow extension (Fig. 7.5). (A) Arrow in overhead view shows the direction of force to self-mobilize elbow extension-adduction (E-Ad). (B) Anterior view shows that with the hand fixed in the partial weight-bearing position, the force applied to the elbow simultaneously extends and adducts the distal forearm relative to the upper arm.

isometric elbow flexion for the C6 myotome was also rechecked and was now full strength and pain-free.

Treatment continued with right unilateral A-P mobilization of C5–C7, but the arm position for preloading the neural tissues was changed to mimic $ULNT_{RADIAL}$ (20 degrees shoulder abduction, shoulder internal rotation, elbow extension and forearm pronation) (Vicenzino et al., 1996). After cervical mobilization, passive elbow extension remained 5 degrees from full extension but was less painful. Passive elbow extension-adduction and A-P and P-A glides of the radial head were unchanged. Large-grip pressure had increased and was less painful. $ULNT_{RADIAL}$ had improved so that lateral elbow pain was not provoked until 20 degrees of shoulder abduction (45 degrees shoulder abduction on left). Treatment was progressed by substituting Grade III and IV right elbow extension-adduction for A-P mobilization of the radial head. Lateral elbow pain was provoked in rhythm with each oscillation. After elbow extension-adduction mobilization, active and passive elbow extension were near full range with less lateral elbow pain. A-P and P-A glides of the radial head were much less stiff and no longer painful. Large-grip pressure was again improved and less painful. $ULNT_{RADIAL}$ was unchanged. Henry continued with the active craniocervical flexion exercise with the arm in abduction. However, self-mobilization of elbow extension in partial weight bearing was modified so that Henry mobilized into elbow extension-adduction (Fig. 7.6). Provocation of lateral elbow pain at the end range of the self-mobilization technique was permitted.

Reasoning Question:

7. Selection and progression of treatment is a largely unresearched area of clinical practice. Would you discuss the general reasoning guiding your approach to 'treatment selection and progression'? Please also comment on your decision to mobilize articular structures (cervical, elbow) rather than the ULNT movements themselves.

Answer to Reasoning Question:

As mentioned previously, treatment focused on reducing signs of sensitivity in lateral elbow and neural structures, rather than trying to change tendon pathology (Coombes et al., 2015). Additionally, we needed to find different treatment strategies because Henry had not responded to previous management. The principle of 'treat and re-assess' guided treatment selection and progression (Maitland 1986, 1991). Relevant impairments (i.e. 'comparable findings' (Maitland, 1991) were treated, and re-assessment determined whether treatment was effective and indicated when changes were needed. The relevance of each impairment was judged by whether it was (1) present in a structure that was within the area of elbow symptoms (e.g. grip force, radial head glides) or able to influence the area of elbow symptoms (e.g. right unilateral A-P pressures from C5 to C7); (2) significant enough to 'fit' with Henry's report

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