CHAPTER 12

Workplace and Other Overuse Injuries

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Musculoskeletal disorders in the workplace have accounted for one-third of occupational illnesses associated with lost work time in U.S. private industry since the mid-1990s (e.g., Bureau of Labor Statistics databases) and cost U.S. health care consumers tens of billions of dollars annually. The prevalence rate of work-related musculoskeletal disorders was 53% in the European Union in the late 1990s (Dupre 2001); and in Canada in 2005, as many as 41% of work-related injuries and disorders resulted from overexertion during pulling, pushing, lifting, or carrying objects (e.g., Alberta Human Resources and Employment 2006 databases).

Epidemiological research has elucidated ergonomic risk factors associated with the development of work-related musculoskeletal disorders (WMSDs). These risk factors include (1) highly repetitive motions; (2) forceful motions; (3) awkward postures, particularly those that are static or at extremes of joint range of motion; (4) prolonged and forceful mechanical coupling between the body and the work environment, as in leaning against or pounding on an object; (5) vibration, either of the whole body (as in standing in a vibrating environment) or of limb segments (as in holding a power tool); (6) cold temperatures; (7) poor lighting; and (8) psychosocial stress involving time pressure, low control over work pace or decisions, or difficult relationships with supervisors or coworkers (National Research Council and Institute of Medicine 2001). Obviously, the etiology of WMSDs is multifactorial, and many workers experience multiple risk factors. Activities outside of work may also contribute to the development of WMSDs through the same mechanisms, leading to an increase in risk or severity of a disorder or both.

While the ideal management of WMSDs would include prevention through the reduction of known risk factors, it is difficult to protect workers from risk factors in the workplace and elsewhere. Health care providers may not have the opportunity to intervene preventively but must respond to a worker's problems long after the initiating risk factors were encountered or after prolonged risk factor exposure. Therefore, clinicians must understand the pathophysiological injury mechanisms stimulated by workplace risk factors.

Muscle Response to Injuries

Muscle injury is described extensively in chapters 1, 3, and 4. Injury to most cell types is reversible; if the insult is mild and short-lived, the cell may be able to withstand the insult and completely return to normal (Banasik 2000). If the insult is mild and persistent, or both, a structural or functional change may occur within the cell and surrounding tissues to enable these structures to withstand the ongoing stress (adaptation). Sometimes, though, the insult is so severe, prolonged, or repetitive that cell death occurs (irreversible cell injury; degeneration). The extent of cell injury depends on the severity and duration of the insult and also on the prior condition of the cell and surrounding tissues. Well-nourished and -adapted cells and tissues may withstand injury better than aged or only partially repaired cells and tissues. Another key reaction of cells and tissues to injury is inflammation, which leads toward regeneration or repair if it is not too extreme.

Chapter 12 Abbreviations

ATP—adenosine triphosphate
Ca^{2+}—calcium ion
CRP—C-reactive protein
ECM—extracellular matrix
ECRB—extensor carpi radialis brevis
EMG—electromyogram
H_2O_2—hydrogen peroxide
IL-1α—interleukin-1 alpha
IL-1β—interleukin-1 beta
IL-6—interleukin-6
Na^+-K^+—sodium-potassium pump
NSAID—nonsteroidal anti-inflammatory drug
O_2^-—superoxide
OH^-—hydroxyl radical
TNF-α—tumor necrosis factor alpha
UBMA—upper body musculoskeletal assessment
WMSD—work-related musculoskeletal disorder

The common reactions to injury in skeletal muscle may or may not be beneficial to the individual cells within the muscle tissue (figure 12.1). Adaptive, beneficial responses include hypertrophy (increased cell size) and fiber splitting. Nonbeneficial reactions include atrophy (decreased cell size) and necrosis (cell death). Three other reactions—inflammation, repair, and regeneration and remodeling—often overlap and are described in chapters 4 and 6. The major benefit of an inflammatory response, as discussed in chapter 4, is to promote clearance of dead cells and debris as well as repair of damaged myofibers and surrounding tissues. However, as discussed later in this chapter, an inflammatory response can also be harmful to healthy cells and tissues surrounding an injury site if it is not kept in check.

Hypertrophy (enlargement of muscle fibers via addition of newly constructed myofibrils) is a common response to increased physiological demands on muscle. Such adaptive responses, which are discussed in chapter 6, lead to increased skeletal muscle mass and strength. Muscle cells may return to their normal size after the increased demand has ended. However, muscle tissue may not completely return to its original size because of persistent structural changes in the surrounding connective tissues.

Atrophy may result from chronic disuse, denervation, ischemia, nutrient starvation, persistent cell injury, or aging (for review, see Allen et al. 1999). Disuse atrophy occurs in skeletal muscle with prolonged reduction in use, for example after extended bed rest or immobilization or in chronic joint disease. Denervation atrophy occurs following loss of innervation of a muscle. This type of atrophy results in losses in individual muscle fibers, decreasing the overall skeletal muscle size. A sublethal and chronic hypoxia also results in cell atrophy, although full-blown ischemia leads to cell death. Poor blood supply to muscles can lead to chronic nutrient starvation; poor diet and nutrient distribution can also cause cellular starvation. Persistent cell injury from chronic inflammation can lead to muscle atrophy as well.

Hypoxia usually results from inadequate blood delivery. Blood vessel injuries cause blood loss and thus cellular hypoxia. Another cause of hypoxia is a prolonged mechanical deformation of tissues leading to an obstruction of blood flow. Decreased intracellular oxygen delivery to the mitochondria can stall cellular adenosine triphosphate (ATP) production and ATP-dependent pumps, including Na^+-K^+ and Ca^{2+} pumps. Ischemia-reperfusion injury results in cell hypoxia and the abnormal generation of reactive oxygen molecules (oxygen free radicals) in and around the cells (see Gute et al. 1998). Reactive oxygen species, such as superoxide (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH^-), damage cell membranes, denature proteins, disrupt cell chromosomes, and help initiate inflammatory cascades. White blood cells recruited to the area release lytic enzymes, additional oxygen free radicals, and other chemicals that further damage cells in the area. Irreversible cell injury occurs when the insult is so severe or prolonged that the cells are unable to adapt or to repair themselves.

Cellular and physiologic responses of muscle to injury induced by single bouts of exercise are covered in chapter 4. Other types of muscle injury, such as repeated microtrauma, result in fibrosis (Stauber et al. 1996) and chronic inflammation (Barbe et al. 2003), which further drives the fibrotic response. Stauber and colleagues (1996) found that repeated cycles of muscle strain at fast rates resulted in intercellular-extracellular matrix thickening (evidenced by increased fibronectin deposition) and the formation of intercellular collagen struts. Nikolaou and colleagues (1987) also observed fibrotic repair (fibroblast granulation tissue in repaired zones) after muscle strain injury despite resolution of a previous inflammatory process. Fibrotic repair generally leads to reduced biomechanical strength. In the following section we review experimental findings in animal models of WMSD, as well as findings from humans with these disorders.

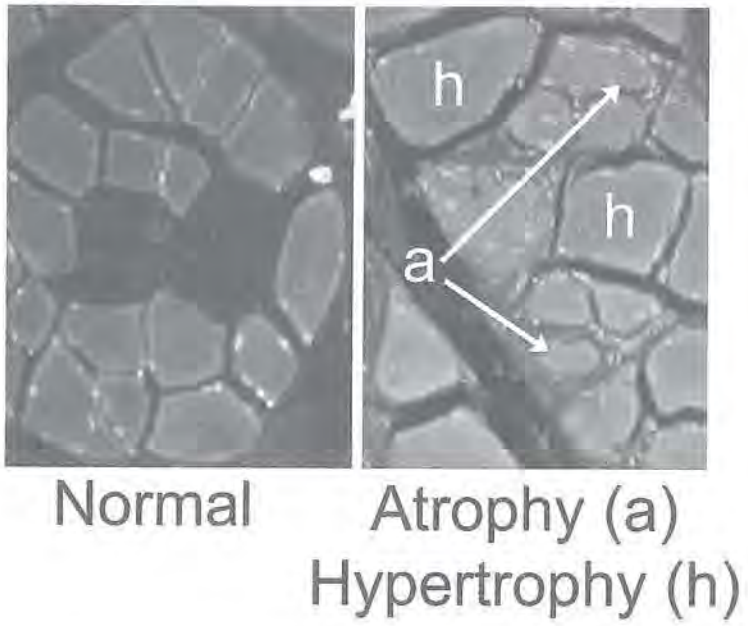

Figure 12.1 Photos showing *(a)* normal muscle in cross section compared to *(b)* denervated and contracted muscle, which contains both atrophied and hypertrophied myofibers.

Workplace- and Overuse-Related Muscular Disorders

To the extent possible, we discuss experimental findings in animals that have been corroborated by recent studies in humans. The use of animal models is particularly important in research on the early development of WMSDs because of lack of access to the tissues of healthy, nondisabled workers with preclinical symptoms. It is the early tissue changes that may provide clinicians and ergonomists with the necessary clues to prevent future, irreversible tissue damage.

Research Using Animal Models

Substantial work over the past two decades has elucidated the mechanisms of muscle injury and their relationship to the type, magnitude, and frequency of contractions. To summarize, eccentric (i.e., lengthening) contractions, particularly of high frequency, produce greater direct and indirect injury, inflammation, and long-term structural tissue changes (refer to chapters 1, 2, and 5) than other types of contractions. While high-magnitude contractions worsen muscle injury and its sequelae, even low-magnitude contractions may induce pathophysiological changes, particularly if they are performed over a period of weeks to months. In this section we discuss key findings on injury, inflammation, and repair and degeneration in muscle tissues in animal models of WMSD or repetitive motion. Table 12.1 lists the findings from various animal models of muscle damage due to repetitive motion.

Nonvoluntary Repetitive Motion Injury Model

Forced lengthening through a physiological range of motion of rat soleus or tibialis anterior muscle during electrical stimulation to tetany leads to injury in as few as five sets of 10 stretches (Fritz and Stauber 1988) and shows a dose-dependent increase in muscle damage between 0 and 300 stretches (Hesselink et al. 1996). Evidence for such injury includes myofiber disruption as well as extracellular matrix (ECM) changes that evolve over a five-day period postexercise. Within 24 h, mononuclear cells are detected, and myofibers take on a swollen appearance with centralization of nuclei (Hesselink et al. 1996). Thereafter, myofibers undergo loss of cross-sectional area (i.e., retraction) with subsequent widening of the interstitial spaces between myofibers, which is evidence of injury-induced edema. By 48 h postexercise, a shift from sulfated to unsulfated proteoglycans and the presence of heparin sulfate in the ECM of muscle tissue indicate that myogenesis has begun. At five days, sulfated proteoglycans again are observed and heparin sulfate undergoes degeneration, suggesting a conclusion to the repair process.

The significance of the findings regarding the ECM molecules, proteoglycans and heparin sulfate, lies in their regulatory function in inducing myogenesis and

Table 12.1 Selected Animal Studies of WMSDs and Repetitive Motion Showing Effects on Muscle Tissues

Authors	Model and protocol	Findings for each study categorized based on tissue and functional changes
Stauber et al. 1994; Stauber et al. 1996	Rat: forced lengthening of soleus muscle at slow (10 mm/s) or fast (25 mm/s) strain rates, 3/week for 4-6 weeks	[3]Hypertrophy, ↑muscle mass, ↑myofiber area (adaptation) after slow stretch; [1 or 3]↑muscle mass, ↓myofiber area after fast stretch; [3 or 4]myofiber splitting and ↑type II A fibers (regeneration) after fast stretch; [5]collagen struts after slow stretch; [4]clear fibrosis after fast stretch
Stauber et al. 2000	Rat: forced lengthening of tetanus toxin–induced hyperactive soleus muscle 50 strains/day, 5/week for 6 weeks, followed by 3 months of cessation of toxin-induced hyperactivity and normal cage activity	[2]Hypervascularity; [3]↓muscle mass, ↓myofiber area; [4 & 5]↑noncontractile tissue, ↑collagen content; [5]incomplete recovery of tissue changes after 3 months
Barr et al. 2002	Rat: reaching and grasping task, 1 reach/30 s, 45 mg of force 2 h/day, 3 days/week for 12 weeks	[2]No increase in serum IL-1α (only serum examined); [6]no motor changes
Barr, Amin, Barbe 2002; Barr et al. 2002; Barbe et al. 2003; Clark et al. 2003	Rat: reaching and grasping task, 1 reach/15 s, 45 mg of force 2 h/day, 3 days/week for 8-12 weeks	[1 & 4]↑hsp72 in distal forelimb and palm by week 3, nerve demyelination beginning week 9; [2]bilateral ↑ in macrophages in nerve and all muscles examined in week 3-6, ↑COX2 and IL-1β in cells of muscles, tendons, CT of distal forelimb and palm, ↑serum IL-1α; [4]bilateral ↑intraneural fibrosis (CTGF and collagen type I) in weeks 8-12; [6]↓NCV of median nerve of reach limb in weeks 9-12, ↓reach rate and task participation, maladaptive movement pattern (raking) beginning in week 4
Clark et al. 2004	Rat: reaching and grasping task, 1 reach/15 s, 180 g of force 2 h/day, 3 days/week for 12 weeks	[2]Bilateral ↑ in macrophages in median nerve; [4]bilateral ↑ intraneural fibrosis (CTGF and collagen type I); [6]bilateral ↓NCV of median nerve, ↓reach rate and task duration, maladaptive movement pattern (raking), bilateral ↑paw withdrawal response threshold to tactile stimulation, bilateral ↓grip strength
LeMay et al. 1990	Rat: exposed to open-field stress (placement in large, bright white pen) 15, 30, or 60 min/day for up to 10 days	[2]↑Serum IL-6 at all exposure times compared to nonexposed controls; [2]↑serum IL-6 positively correlated with stress exposure time; [2]↑body temperature above controls with stress 30 and 60 min exposures; [3]adaptation of IL-6 and body temperature with repeated stress exposures (days 9 and 10)
Hesselink et al. 1996	Rat: isometric or eccentric (forced lengthening) of tibialis anterior 20 times/min for 3-15 min (60-300 contractions)	[1 & 2]↑Fiber swelling, centralization of nuclei, infiltration of mononuclear cells in eccentric exercise of 180 contractions and greater; [1]↑fiber swelling in isometric exercise with 300 contractions; [6]↓peak isometric torque after 60 contractions in eccentric more than isometric
Fritz and Stauber 1988	Rat: forced lengthening of soleus 5 × 10 repetitions with 15 s rest between bouts	[1]↓Chondroitin 6-sulfate around damaged fibers through 72 h postexercise, ↑concanavalin A in interstitial space; [4]↑unsulfated chondroitin proteoglycans around damaged fibers at 48 h postexercise, ↑heparan sulfate around damaged fibers at 72 h postexercise

[1]Injury/degenerative changes; [2]inflammatory/proliferative changes; [3]adaptive tissue changes/tissue reorganization; [4]repair ± regeneration or scarring (fibrosis); [5]pathological remodeling; [6]functional changes (e.g., behavioral or biomechanical).

Abbreviations: COX2 = cyclooxygenase 2; CT = loose areolar and synovial connective tissue; CTGF = connective tissue growth factor; hsp72 = inducible form of heat shock protein 70/72; IL-1α = interleukin-1 alpha; IL-1β = interleukin-1 beta; NCV = nerve conduction velocity; WMSD = work-related musculoskeletal disorder.

providing the scaffolding for proper myofiber orientation during the repair process. Of further significance is the observation that, if given sufficient time without subsequent injurious activity, muscles will undergo effective repair and restoration to their preinjury state or even hypertrophy. However, repetitive motion injury differs substantially from the acute muscle injury model just described; it involves low-magnitude contractions of all types (isometric, concentric, and eccentric), at a high frequency, performed over long periods (i.e., weeks to months). Several investigators have adapted animal models to study the pathophysiology of muscle injury resulting from low-intensity repetitive motion.

In a modified eccentric loading protocol using their rat soleus model, Stauber and colleagues (1994, 1996) studied the effects of both fast (five bouts of 10 repetitions in 5 s) and slow (five bouts of 10 repetitions in 13 s) stretching for three days per week for one month. The slow- and fast-stretch groups showed an increase in soleus muscle mass of 12.8% and 10.4%, respectively. The muscle mass increase in the slow-stretch group was accompanied by muscle hypertrophy and collagen strut formation in the ECM—both indicators of tissue adaptation to increased applied load. On the other hand, the muscle mass increase in the fast-stretch group was accompanied by a widening of interstitial space, increased variability in muscle fiber size with an increase in the number of small and type II A fibers, fiber splitting, infiltration of inflammatory cells (macrophages), and fibrosis. These pathological changes have similarities to those of myopathic diseases and are indicative of a lack of adaptation. The presence of small myofibers, for example, raises the possibility that the fast-stretch muscles are undergoing regeneration or failed healing due to the inability of the normal repair process to keep pace with the repeated muscle injury. This finding represents the essence of repetitive motion injury: The persistent presence of an injury stimulus outpaces tissue repair. Furthermore, recovery from such pathophysiological changes has been shown to be slow, even with complete cessation of the repeated strains for a period of three months (Stauber et al. 2000)—thus highlighting the importance of prevention in the management of such disorders. To cite one example of a preventive measure, Stauber and Willems (2002) compared histopathological evidence of muscle damage in their rat model of forced lengthening using two different interstretch rest breaks, long (180 s) and short (40 s). The longer rest break between stretches prevented such histopathological changes, while the shorter rest break resulted in evidence of muscle damage.

Voluntary Repetitive Motion Injury Model

The finding by Stauber and colleagues of inflammatory cells in injured muscle tissues was not surprising. Yet the presence of inflammation in repetitive motion injury has not been clearly described with respect to its dose dependence, onset, contribution to signs and symptoms, and role in tissue repair or fibrosis. Work in our laboratory has focused on the inflammatory response to repetitive motion injury of numerous tissues, including muscle, tendon, peripheral nerve, bone, and serum, in a model of repetitive reaching and grasping in the rat (Barbe et al. 2003; Barr and Barbe 2002, 2004; Barr et al. 2002, 2004a, 2000, 2003; Clark et al. 2003, 2004). Unlike previous models of repetitive motion, our model uses a voluntary and functional movement regimen with postural and exposure constraints that permits us to observe behavior as well as to examine tissues in response to different levels of task demands (see Barbe et al. 2003). While we cannot control the loading protocol to the same level of precision as the previously described models, we can use such studies as a frame of reference for interpreting the nature and magnitude of our tissue findings. What we gain by not controlling task exposure precisely is a holistic model that allows observation of animal behavior in response to task exposure.

Using this model we have demonstrated that localized inflammation of injured distal forelimb muscles of the reach limb begins within three weeks of a highly repetitive (8-12 reaches per minute), low-force (<10% maximum voluntary grip force) reaching regimen. Evidence of muscle injury includes the presence of the inducible form of heat shock protein 72 (an indicator of cell distress) and fray at the myotendinous junction of the long digital flexors of the forelimb (an indicator of mechanical stress; figure 12.2) (Barr et al. 2000; Barbe et al. 2003). Inflammatory changes include increased numbers of infiltrating, phagocytic macrophages in the lumbrical muscles, long digital flexors, and surrounding loose connective tissues, which peak at five weeks of task performance. We also observed increased expression of the proinflammatory cytokine interleukin-1 alpha (IL-1α), which peaks between three and five weeks of task performance (figure 12.3), and increased expression of cyclooxygenase-2, a proinflammatory mediator in the arachidonic acid pathway that produces prostaglandins with free radicals as by-products. Free radicals have been implicated in progressive vascular damage and cytotoxicity, thereby worsening pathology in tissues experiencing a prolonged inflammatory response. Prostaglandin E_2 has been implicated in muscle pain.

The muscle injury observed in our model is accompanied by a local inflammatory response in the form of increased infiltrating macrophages (Barbe et al. 2003). This same inflammatory response has also been observed in median nerve tissues of rats performing

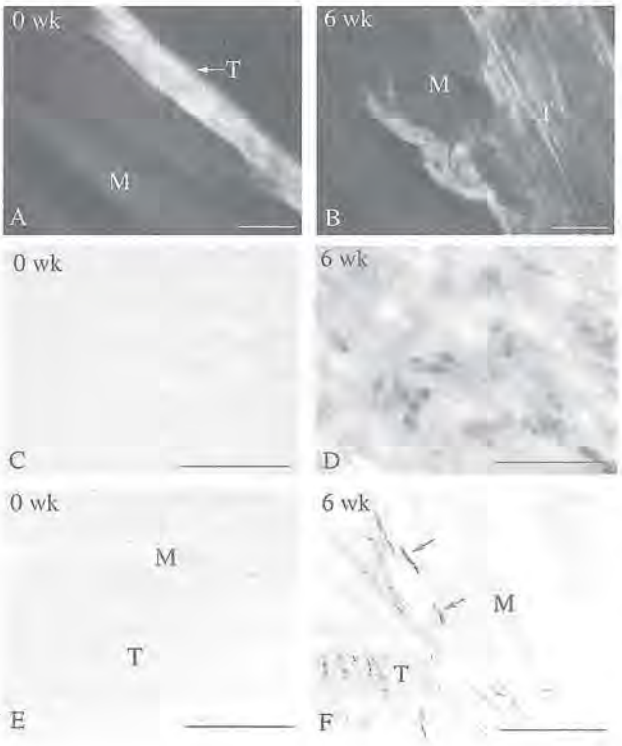

Figure 12.2 Photos showing control rat tissues *(a, c, e)* in comparison to *(b)* microfray at the myofiber-tendinous junction; *(d)* macrophages (dark spots) in connective tissues, *(f)* forelimb flexor muscles, and (inset in *f*) forelimb tendons of rats performing a high-repetition, low-force task for six weeks. M = muscle; T = tendon; arrows indicate macrophages in myofibers at tendon junction. Bar = 50 μm.

From M.F. Barbe et al., 2003, "Chronic repetitive reaching and grasping results in decreased motor performance and widespread tissue responses in a rat model of MSD," *J Orthopedic Res* 21(1): 167-176.

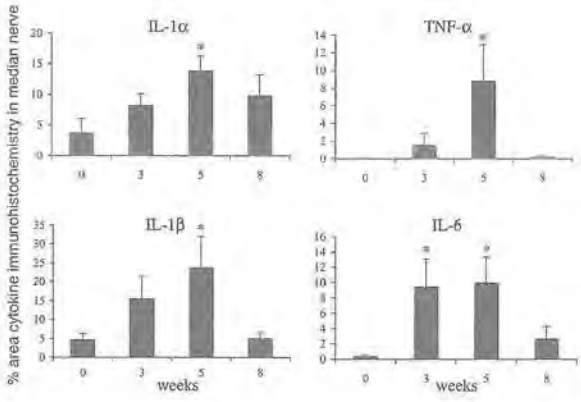

Figure 12.3 The proinflammatory cytokine, IL-1α, increase in median nerve with performance of a high-repetition, low-force task.

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either a highly repetitive low-force or a highly repetitive high-force (50% maximum grip force) task regimen (Clark et al. 2003, 2004). In addition, the median nerve and surrounding tissues show evidence of fibrosis and decreased nerve conduction velocity across the carpal tunnel, with these impairments increasing with increasing task demands (figure 12.4). Results on the dose dependence of the inflammatory responses in muscle tissue are similar to the findings in the median nerve (Barbe et al. submitted).

Behavioral changes consistent with discomfort or movement dysfunction coincide with the tissue changes and also demonstrate dose dependence. These behavioral changes include decreased reach rate (an indicator of animals' inability to maintain task pace), decreased time on the task (an indicator of overall discomfort), and an increase in an abnormal movement pattern known as raking (repeated attempts to reach a target, causing a paradoxical increase in movement repetition) (Barbe et al. 2003; Barr et al. 2000). These behavioral changes begin to emerge as early as three weeks of task performance in a group that performs a highly repetitive and forceful task, and continue to decline through 12 weeks (Barr and Barbe 2004; Clark et al. 2004). With a highly repetitive, low-force task regimen, the behaviors decline at five to six weeks of task performance and then rebound to baseline levels (Barbe et al. 2003; Barr et al. 2000; Barr and Barbe 2004; Clark et al. 2003). When rats perform a task regimen with low repetitions (four to six reaches per minute) and low force, the reach rate and time of task participation do not decline, although the raking behavior does emerge in approximately 50% to 60% of animals by seven weeks of task performance (figure 12.5) (Barr and Barbe 2004; Barr et al. 2002). Taken together with the tissue response, the behavioral changes strongly support findings in the epidemiological literature on WMSDs—that highly repetitive tasks alone are associated with muscle injury and inflammation, with potential long-term tissue scarring and fibrosis, and that the combination of highly repetitive and forceful tasks increases both the tissue response and the ensuing behavioral dysfunction. The finding that task demands can be kept low enough to prevent behavioral changes also suggests that muscle injury may be avoided by reduction in task dose levels.

In addition to the local muscle tissue response induced by our repetitive reaching paradigm in the rat, we have observed evidence of a widespread and even systemic inflammatory response (Barbe et al. 2003; Barr et al. 2002, 2004a). Infiltrating macrophages and proinflammatory cytokines (IL-1α and IL-1β) have been observed in multiple anatomical sites and tissue types (figure 12.6), as well as in serum (figure 12.7)

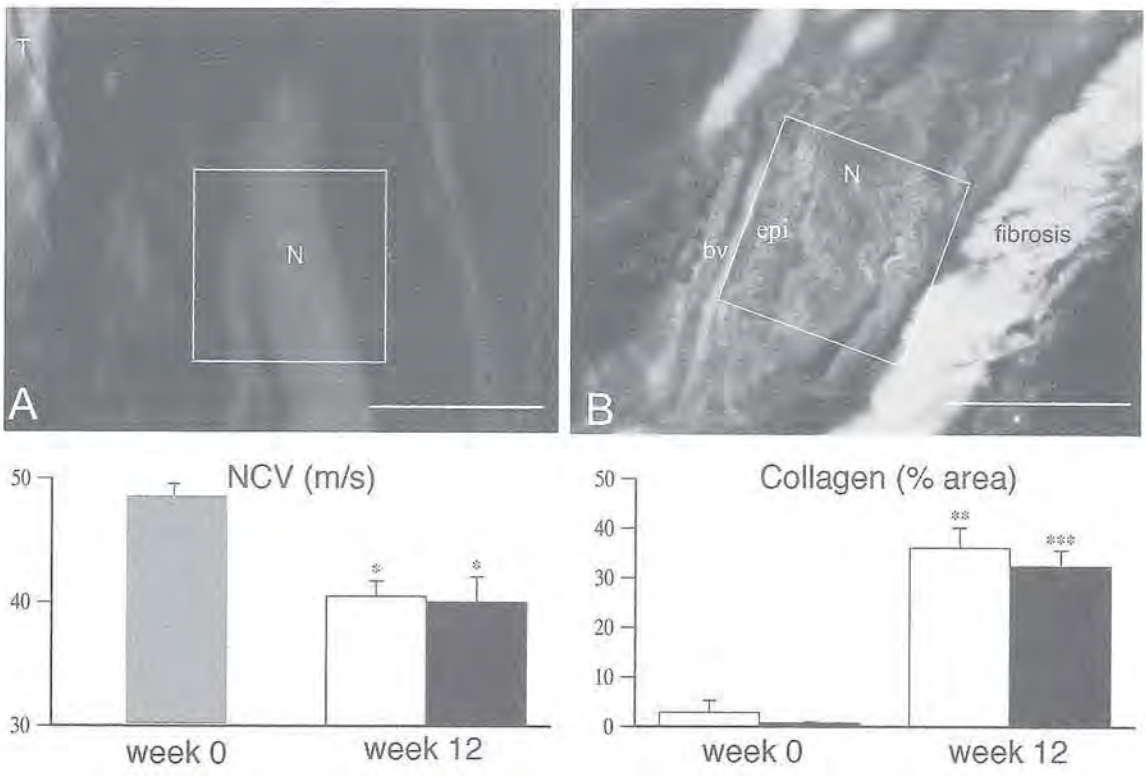

Figure 12.4 Increased collagen type I, indicative of fibrosis, was present in and around the median nerve of *(b)* a 12-week task rat compared to *(a)* a control rat. Nerve conduction velocity (NCV) decreased in median nerves of reach (white bar) and nonreach (black bar) limbs after 12 weeks of performing a high-repetition, high-force task. This decrease coincided with increased collagen around the nerve. $*p < 0.01$; bv = blood vessel; epi = epineurium; N = nerve; bar = 50 μm.

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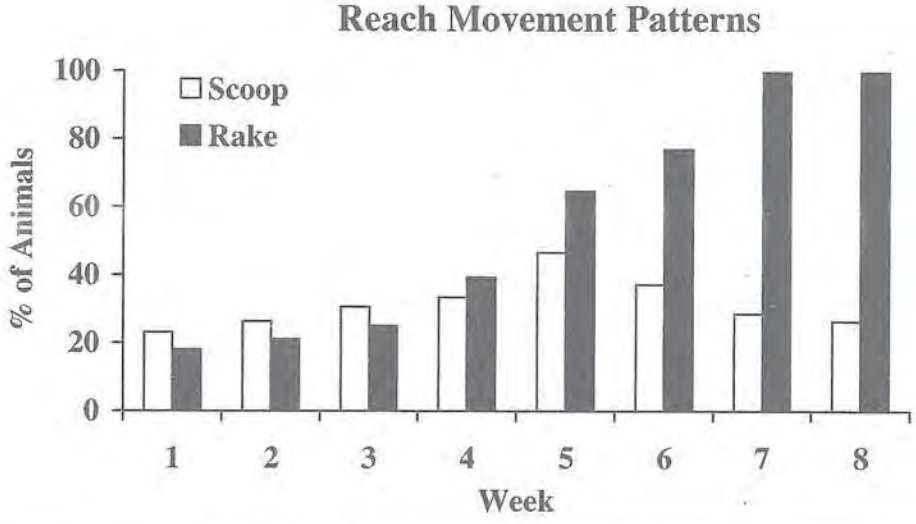

Figure 12.5 A raking-type reaching mode emerged in 100% of the animals by week 7 of performing a high-repetition, low-force task.

From M.F. Barbe et al., 2003, "Chronic repetitive reaching and grasping results in decreased motor performance and widespread tissue responses in a rat model of MSD," *J Orthopedic Res* 21(1): 167-176.

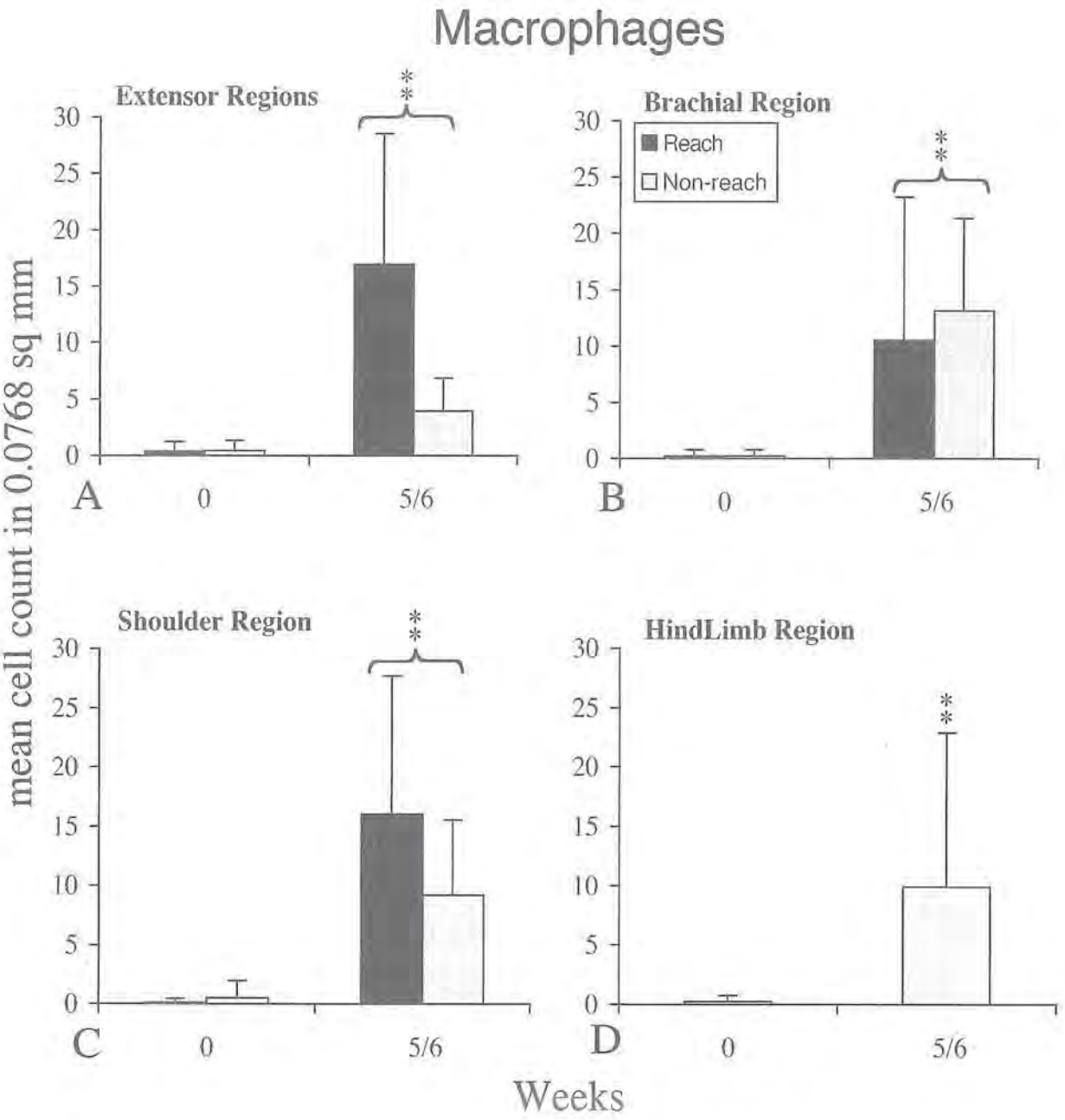

Figure 12.6 The number of macrophages increased in musculotendinous tissues of the forearm extensor, brachial, shoulder, and hindlimb regions after five to six weeks of performance of a high-repetition, low-force task. $^{**}p < 0.001$.

From M.F. Barbe et al., 2003, "Chronic repetitive reaching and grasping results in decreased motor performance and widespread tissue responses in a rat model of MSD," *J Orthopedic Res* 21(1): 167-176.

(Al-Shatti et al. 2005; Barbe et al. 2003). In a quadruped species, the presence of inflammatory mediators in anatomical sites distant from the reach limb may arguably result from localized exposure of these sites due to their participation in the task, but the presence of proinflammatory cytokines in serum is indisputable evidence of a systemic inflammatory response.

We have proposed a mechanism whereby the presence of such a systemic response may lead to amplification of local tissue injury and inflammation through

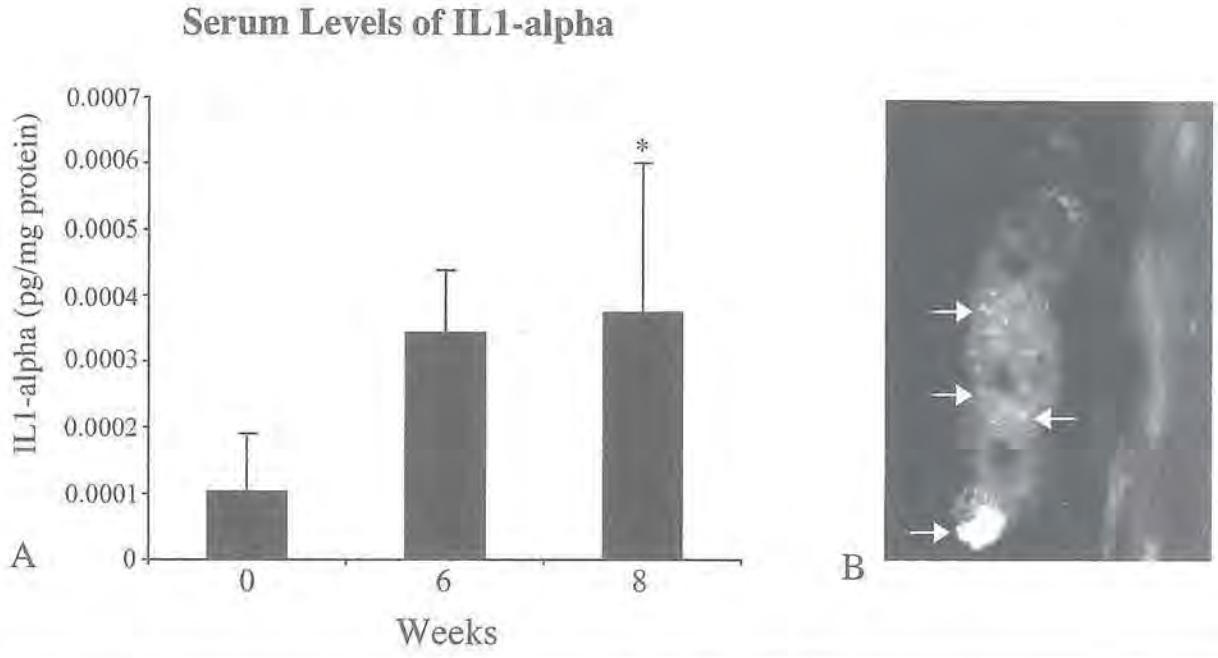

Figure 12.7 *(a)* Serum levels of interleukin-1 alpha (IL-1α) increased significantly in rats during eight weeks of performance of a high-repetition, low-force task compared to controls (*$p < 0.05$). *(b)* Photomicrograph illustrating a muscle macrophage expressing ED-1 immunoreactivity (bright white areas indicated by arrows) that coexpresses IL-1α (gray areas).

From M.F. Barbe et al., 2003, "Chronic repetitive reaching and grasping results in decreased motor performance and widespread tissue responses in a rat model of MSD," *J Orthopedic Res* 21(1): 167-176.

a complex and vicious cycle that renders tissues more susceptible to future injury at constant levels of task demands. In this proposed mechanism, depicted in figure 12.8, a unilateral, repetitive activity induces a localized inflammatory response. If the injury stimulus ceases, an acute inflammatory episode is resolved and healing occurs. If the injury stimulus persists, circulating cytokines will have effects on tissues not directly involved in task performance or global physiological effects. Initiation of the systemic response sensitizes tissues, both local and distant in relation to the injury stimulus, and causes further upregulation of proinflammatory cytokines. Hence the cycle of widespread and chronic effects is propagated.

The "Sickness Response" to Muscle Damage

Also indicated in the proposed mechanism (figure 12.8) is the potential occurrence of global physiological effects due to circulating proinflammatory cytokines. These physiological effects are known as the "sickness response," a constellation of psychoneuroimmunological effects of proinflammatory cytokines, specifically IL-1β, TNF-α, and IL-6, that have been extensively studied in animal models over the past decade. These responses include fever, weakness, listlessness, hyperalgesia, allodynia, decreased social interaction and exploration, somnolence, decreased sexual activity, and decreased food and water intake (Watkins and Maier 1999; Goehler at al. 1997; Kelley et al. 2003; Dantzer 2004). The sickness response is adaptive; that is, it results in behavior that minimizes energy expenditure in order to allocate metabolic resources to fighting infection or disease (Dantzer 2004). Furthermore, the sickness response was shown to be a motivational state with respect to feeding behavior in rats. Aubert and colleagues (1995) demonstrated that rats injected with IL-1β reduced the frequency of lever presses to receive a food reward but readily ate food that was freely presented. From a motivational standpoint these results suggest that IL-1β produces an aversion to foraging, which is an energy-intensive activity, rather than to feeding per se.

The mechanism of action of the proinflammatory cytokines on such behavioral responses has been partly elucidated but is still a subject of intense research. Recent attention has been given to the possible role of proinflammatory cytokines in the etiology of depression and other mood disorders, particularly among cancer patients treated with proinflammatory cytokine therapy (Capuron and Dantzer 2003). Psychological stress in a rat model has been shown to increase serum levels of IL-6, a cytokine implicated in the acute phase response

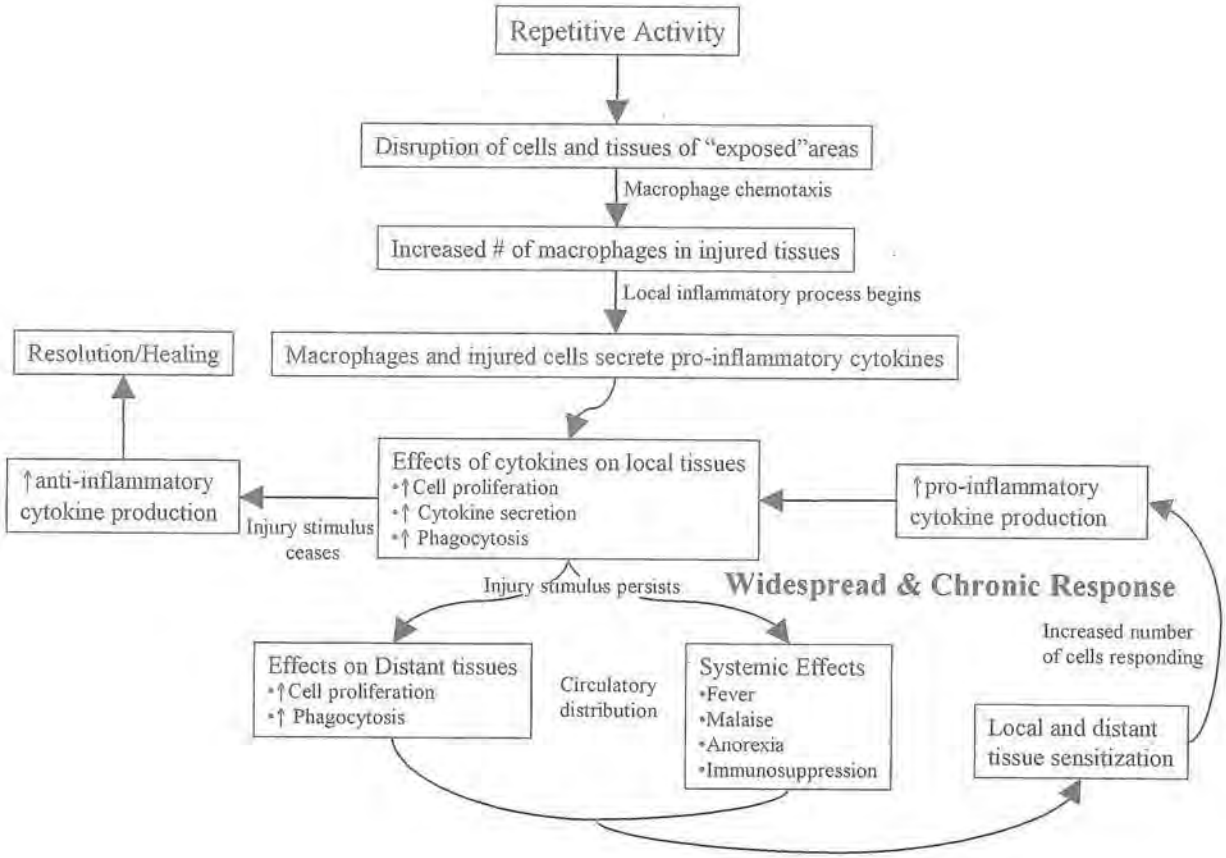

Figure 12.8 Proposed mechanism for the role of systemic distribution of cytokines in widespread WMSD symptoms. ↑ = increase.

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of inflammation (LeMay et al. 1990). The possibility for patients with chronic inflammatory conditions to succumb to the depressive effects of local and systemic proinflammatory cytokines has implications in the management of WMSD. Symptoms of depression and anxiety have been reported in numerous epidemiological and clinical studies of patients with WMSD (e.g., Mathis et al. 1994; Leclerc et al. 2001; Keogh et al. 2000; Weigert et al. 1999). These findings may be attributed to the sickness response, thus suggesting a physiological basis for such symptoms. In our model of repetitive motion injury in the rat, for example, the decreased task participation behavior was accompanied by somnolence, listlessness, and decreased exploration. These behaviors suggest a withdrawal response consistent with sickness behavior. We hope to investigate the relationship between such behaviors and systemic inflammation in future studies in our laboratory.

In summary, animal models of muscle injury, inflammation, and repair in response to repetitive motion tasks have provided rich information regarding the likely mechanisms underlying the development of musculoskeletal disorders in the workplace. These laboratory-based studies have generally supported findings in the epidemiological and clinical literature on workers with WMSD. In the next section, we discuss recent studies in humans that corroborate, to the extent possible, the findings in these animal models.

Research on Humans

Stauber and colleagues (1994) confirmed the mechanisms of injury with maximal eccentric activation as seen in their rat model in a study of biceps brachii in human subjects. Needle biopsies were obtained 48 h after subjects performed 70 maximal isokinetic eccentric contractions

of the elbow flexors through a range of 120° at an angular velocity of 120°/s with a 10 s rest between contractions. In addition to significant increases in pain and decreases in relaxed elbow angle seen at 48 h postexercise, histological examination of the biopsied tissues revealed the interstitial widening and increased sulfated proteoglycans in the ECM characteristic of muscle injury. Furthermore, macrophages were observed in the interstitial spaces near blood vessels and in or near necrotic muscle fibers, which confirmed the onset of a delayed inflammatory response to the muscle injury. In a subsequent study, Gibala and colleagues (1995) observed immediate (within 20 min of maximum eccentric exercise) myofibrillar disruption of human biceps brachii myofibers as evidenced by discontinuities in the normal myofibrillar banding pattern seen with electron microscopy. The proportion and severity of disruption were greater with eccentric than with concentric contractions.

While a number of researchers have studied the characteristics of muscle tissues in patients with WMSD (table 12.2), the challenge lies in understanding the mechanisms leading to those observed changes, which are typically examined late in the process of WMSD development (for a perspective on this topic, see Barr and Barbe 2002). For example, Dennett and Fry (1988) performed open biopsies on affected first dorsal interosseous muscles in patients with WMSD and found histological and ultrastructural changes in muscle fibers consistent with denervation or ischemic loss (or both) of type II muscle fibers and hypertrophy of type I fibers. Larsson and colleagues (1990) demonstrated the presence of cellular pathology, in the form of ragged red myofibers, related to mitochondrial dysfunction in trapezius muscle biopsies from symptomatic assembly line workers who were exposed to static loading of the trapezius. The observed changes were consistent with localized hypoxia and were correlated with reduction in muscle blood flow. In biopsies of extensor carpi radialis brevis (ECRB) muscle from patients with work-related epicondylitis, Ljung and colleagues (1999) observed "moth-eaten" muscle fibers, myofiber necrosis, a shift from type II B to the more oxidative type II A myofibers, and increased evidence of myofiber regeneration. These changes are consistent with adaptation to a relative ischemic state and were postulated by Ljung and colleagues to be caused by chronic overactivity in the ECRB muscle. However, some of the patients in this study had a recent history of underuse of the affected upper limb and of steroid injections into the affected muscle, and it is difficult to rule out the influence of these confounding factors on the observed morphological changes.

Trapezius Injury

The majority of studies in humans showing direct structural or physiological muscle changes have involved the trapezius muscle. This is an important site for work-related myalgia resulting from upper limb–intensive tasks given that this muscle has supportive as well as action roles in upper limb function. It is also a frequently affected region in disorders of this type. In studies of male forest-harvesting machine operators or crane operators with work-related trapezius myalgia, Kadi, Hagg, and colleagues (1998) found hypertrophy of type II A fibers, increased vascularization, moth-eaten fibers, centralization of nuclei, presence of developmental myosin, and accumulation of desmin. All of these changes were considered indicative of pathology. An increase above nonoperator control values in the cross-sectional area of type I and II A fibers among these affected workers, also observed in occupational controls without myalgia, was interpreted as an adaptive hypertrophy indicative of chronic exposure to low-level static loading of the trapezius. In females with work-related trapezius myalgia (Kadi, Waling et al. 1998; Lindman et al. 1991), different findings included an increase in cross-sectional area of only type I myofibers, which was interpreted as a hypertrophic adaptive response, and a low capillary to fiber area ratio for both type I and II A fibers that was directly related to reported intensity of pain and hypothesized to cause oxidative stress in these undervascularized tissues. In both males and females with work-related myalgia, the presence of cytochrome c oxidase–negative muscle fibers suggested an oxidative crisis within muscle cells exposed to chronic work-related loading, perhaps through hypoxia (for a review, see Hagg 2000).

An impressive series of studies addressed numerous morphological and physiological muscle changes in female cleaners with trapezius myalgia (Lindman et al. 1991; Larsson, Björk, Elert, and Gerdle 2000; Larsson, Björk, Henriksson et al. 2000; Larsson et al. 2001; Rosendal, Blangsted et al. 2004; Rosendal, Larsson et al. 2004; Larsson et al. 2004). In addition to the morphological evidence for myofiber damage (e.g., moth-eaten fibers; ragged red fibers, characterized by a subsarcolemmal and intermyofibrillary accumulation of mitochondria that appear red with Gomori trichrome stain), the investigators found a decrease in the cross-sectional area of type II fibers (in contrast to the studies discussed in the preceding paragraph) and a correlation between the proportion of ragged red fibers and type I fibers. They also found evidence of cytochrome c oxidase–negative fibers, but these were present in all groups (cleaners with myalgia, cleaners without myalgia, and noncleaner controls) (Larsson, Björk, Henricksson et al. 2000). Regression analysis showed that the prevalence of cytochrome c oxidase–negative ragged red fibers was partly age dependent, irrespective of myalgia.

This last finding is of particular interest given the protective role of estrogen, which stabilizes muscle cell membranes following injury and attenuates leukocyte infiltration in exercise-induced muscle damage (Tiidus 2003; Stupka and Tiidus 2001). The average age of the

Table 12.2 Selected Human Studies of WMSDs and Repetitive Motion Showing Effects on Muscle Tissues

Authors	Subjects and protocol	Findings for each study categorized based on tissue and functional changes
Dennett and Fry 1988	Subjects: 29 pts with painful chronic hand WMSD Measurements: histochemical and morphological examination of first dorsal interosseous biopsies	[2]↑Inflammatory cells; [3]↑type I fibers, ↓number and hypertrophy of type II fibers; [3]mitochondrial changes
Kadi, Hagg, et al. 1998; Kadi, Waling, et al. 1998	Subjects: 21 females with trapezius myalgia (Kadi, Waling, et al.); 10 male machine operators with trapezius myalgia, 9 male machine operators without myalgia, and 6 male healthy controls (Kadi, Hagg, et al.) Measurements: histochemical and morphological examination of trapezius biopsies; pain via VAS	Females: [3]↑CSA and proportion of type I fibers compared to controls from previous study (Lindman et al. 1991); [5]↓capillary: CSA type I fibers in myalgia with high pain scores compared to low pain scores; [5]COX-negative type I fibers > with high pain scores compared to low pain scores Males: [3]↑frequency of type II A fibers; [3]capillarization; [1]centralization of nuclei and developmental myosin in myalgia group compared to controls; [1 & 5]↑mitochondrial disorganization and COX-negative fibers in myalgia group and occupational controls compared to healthy controls
Larsson et al. 1990	Subjects: 17 female assembly workers with work-related trapezius myalgia Measurements: histochemical and morphological examination of trapezius biopsies; local blood flow via laser-Doppler flowmeter	Histological: [1]moth-eaten fibers and ragged red type I fibers worse on more painful side; [1]centralization of fiber nuclei; [1]atrophic fibers; [4]fiber splitting Blood flow: [1 & 5]↓blood flow positively correlated with pain and ragged red fibers
Larsson, Björk, Henriksson, et al. 2000; Larsson et al. 2004	Subjects: 25 female cleaners with work-related trapezius myalgia (CM), 25 female cleaner controls without TM (CC), 21 healthy female teacher controls (TC) Measurements: histochemical and morphological examination of trapezius biopsies	[5]↓Capillary:fiber CSA in CM compared to CC; [1]moth-eaten fibers in CM and CC (4%) > TC (2%); [1]prevalence of ragged red fibers related to working as a cleaner and having tender point in trapezius; [5]COX-negative fibers correlated with age regardless of occupation
Larsson, Bjork, Elert, and Gerdle 2000; Larsson et al. 2001	Subjects: 25 female cleaners with work-related trapezius myalgia (CM), 25 female cleaner controls without TM (CC), 21 healthy female teacher controls (TC) Exercise: 150 maximum isokinetic shoulder flexions through full ROM at 1.05 rad/s Measurements: histochemical and morphological examination of trapezius biopsies, EMG_{RMS}, EMG_{MPF}, RPE, shoulder flexion isokinetic strength and endurance	[6]Functional: strength CM and CC > than TC; [6]endurance CM < CC and TC, RPE CM > TC > CC, ↓relaxation (i.e., ↑EMG_{RMS}) during passive shoulder extension in CM and CC and decreased with increasing age Histological: [3]↓type II fiber CSA in CM and CC compared to TC; [3]difference between CSA of type I and type II fibers greater in CM and CC than in TC; [1]prevalence of ragged red fibers positively correlated with proportion of type I fibers Correlation between functional and histological: [1]prevalence of ragged red fibers correlated with EMG_{MPF}; [1, 3, 6]prevalence of ragged red fibers, age, fiber type proportion and CSA, and occupation were significant regressors of inability to relax during passive shoulder extension
Lindman et al. 1991	Subjects: females with chronic trapezius myalgia and healthy female controls Measurements: histochemical and morphological examination of trapezius biopsies	[3]↑Type I fiber CSA; [5]↓capillary:CSA for type I and II fibers; [1 or 5]↓ATP and ↓phosphocreatine in type I and II fibers in pts compared to controls

(continued)

Table 12.2 *(continued)*

Authors	Subjects and protocol	Findings for each study categorized based on tissue and functional changes
Ljung et al. 1999	Subjects: 26 pts with lateral epicondylitis >7 months Measurements: histochemical and morphological examination of ECRB muscle biopsies	[1 or 5]Abnormal muscle NADH staining, muscle necrosis; [2]no evidence of muscle inflammation; [3]↑type II A fibers and muscle fiber regeneration
Nemet et al. 2002	Subjects: 23 healthy adults (15 male and 8 female) Exercise: 10 min of unilateral wrist flexion at 40% MVC Measurements: serum metabolites, catecholamines, growth factors, PBMCs, adhesion molecules, and cytokines sampled via heparin-lock catheter from exercised and nonexercised forearms	Postexercise: ↑lactate in exercise arm only; [3]↑GH, Epi (> in exercise arm), Norepi (> in nonexercise arm); [3]VEGF; [2 or 3]IL-6; [2]IL-1ra and [2]PBMCs in both arms; [4]↓FGF-2 in both arms, no gender differences Postexercise recovery period: ↓lactate to BL at 60 min; [3]peak GH level at 10 min and ↓ to BL at 120 min; [3]↓Epi to BL at 30 min; [3]peak Norepi at 10 min, remained slightly elevated at 120 min; [2]↑ VEGF; [2 or 3]IL-6 and [2]IL-1ra continued through 120 min; [4]↓PBMCs to BL at 30 min; [4]↑FGF-2 at 120 min
Rosendal, Larsson, et al. 2004	Subjects: 20 healthy females, 19 females with trapezius myalgia Exercise: 20 min repetitive, low-force exercise (placement of wooden pegs in a desktop peg board) Measurements: microdialysis measurement of interstitial metabolites, pain and PPT, blood flow	Preexercise: [1 or 5]↑lactate, pyruvate, glutamate, serotonin, and pain in myalgia group; [6]↓PPT in myalgia group; [5 & 6]serotonin correlated to pain and glutamate correlated to pain and PPT in myalgia group Exercise: [1 or 5]↑lactate and pyruvate in myalgia group, but not in control group; [5]↑glutamate in both groups Postexercise: [5]↑blood flow and ↑pyruvate prolonged in myalgia group; [4]lactate returned to BL in myalgia group; [4]glutamate returned to BL in both groups
Rosendal, Blangsted, et al. 2004; Rosendal, Sogaard et al. 2004	Subjects: 6 healthy males Exercise: 20 min repetitive, low-force exercise (placement of wooden pegs in a desktop peg board) Measurements: microdialysis measurement of interstitial metabolites and IL-6, serum metabolites and IL-6, EMG_{RMS}, EMG_{MPF}, RPE	Exercise: [6]↑EMG_{RMS} and RPE, lactate; [1]potassium and [2 or 3]IL-6; [6]↓EMG_{MPF} Postexercise: ↑lactate and [1]potassium for 10 min, returned to BL by 20 min; [1]↑pyruvate 20 min postexercise; [2 or 3]peak IL-6 levels 30 min postexercise; serum IL-6 nonsignificantly increased 45%
Stauber et al. 1990	Subjects: 3 healthy males and 2 healthy females Exercise: 70 maximal isokinetic, eccentric movements of the elbow flexors through 120° ROM at 120 °/s Measurements: perceived soreness, relaxed elbow joint angle, histochemical and morphological examination of biceps brachii biopsies	[6]Functional: progressive ↑perceived soreness immediately and 48 h postexercise, progressive ↓relaxed elbow joint angle immediately and 48 h postexercise Morphological: [1]↑area of interstitial space; [1]presence of mononuclear cells and [1]degranulating mast cells; [1]necrotic fibers (2%) Histochemical: [1]↑albumin and fibrinogen in widened interstitial space and in damaged fibers; [4]↑chondroitin 6-sulfate and chondroitin 4-sulfate proteoglycans and concanavalin A in widened interstitial space

(continued)

Table 12.2 *(continued)*

Authors	Subjects and protocol	Findings for each study categorized based on tissue and functional changes
Gibala et al. 1995	Subjects: 8 healthy males Exercise: resisted eccentric movements of elbow flexors using dumbbell on one side, resisted concentric movements of elbow flexors on other side Measurements: low-velocity and high-velocity isokinetic strength and isometric strength of biceps brachii; PTT, TPT, HRT, and MRD via percutaneous stimulation of biceps brachii; EMG_{RMS}; morphological examination of biceps brachii biopsies	[6]Functional: ↓isometric and low-velocity and high-velocity isokinetic strength concentric arm immediately postexercise, ↓isometric and low-velocity isokinetic strength eccentric arm for 96 h postexercise, ↓high-velocity isokinetic strength eccentric arm for 72 h postexercise, ↓isometric and low-velocity isokinetic strength eccentric arm compared to concentric arm for 96 h postexercise, ↓high-velocity isokinetic strength eccentric arm compared to concentric arm 72 h postexercise, ↓PTT and MRD concentric arm immediately postexercise, ↓PTT and MRD eccentric arm for 96 h postexercise, ↓HRT eccentric arm for 48 h postexercise, PTT and MRD concentric arm > eccentric arm for 96 h postexercise, EMG_{RMS} eccentric arm < concentric arm during exercise Morphological: [1]↑fiber disruption in both concentric and eccentric arm immediately and 48 h postexercise; [1]fiber disruption greater eccentric arm compared to concentric arm immediately and 48 h postexercise Relationship between functional and morphological changes: [6]%↑isokinetic strength in eccentric and concentric arms correlated with [1]% severely disrupted fibers 48 h postexercise

[1]Injury/degenerative changes; [2]inflammatory/proliferative changes; [3]adaptive tissue changes/tissue reorganization; [4]repair ± regeneration or scarring (fibrosis); [5]pathological remodeling; [6]functional changes (e.g., behavioral or biomechanical).

Abbreviations: ATP = adenosine triphosphate; BL = baseline; COX = cytochrome c oxidase; CSA = cross-sectional area; ECRB = extensor carpi radialis brevis; EMG_{MPF} = mean power frequency electromyography; EMG_{RMS} = root mean square electromyography; Epi = epinephrine; FGF-2 = fibroblast growth factor; GH = growth hormone; HRT = one-half relaxation time; IL-1ra = interleukin-1 receptor antagonist; IL-6 = interleukin-6; MRD = maximum rate of torque development; MVC = maximum voluntary contraction; NADH = nicotine adenine dinucleotide reductase; Norepi = norepinephrine; PBMCs = peripheral blood mononuclear cells; PPT = pressure pain threshold; pts = patients; PTT = peak twitch torque; ROM = range of motion; RPE = rating of perceived exertion; TPT = time to peak torque; VAS = visual analog scale for pain perception; VEGF = vascular endothelial growth factor; WMSD = work-related musculoskeletal disorder.

cleaners in the studies by Larsson and Lindman was 46 ± 10 years, placing the older subjects in the menopausal or postmenopausal age range. Therefore, the finding of myofiber distress (as indicated by cytochrome c oxidase–negative ragged red fibers) in older subjects may indicate that they lacked protective levels of estrogen. This study also showed that a significantly larger proportion of cytochrome c oxidase–superpositive fibers were also ragged red fibers in women with work-related myalgia, although whether this is an adaptive or a pathological response is still unclear. Point tenderness of the trapezius on palpation was also associated with increased prevalence of ragged red fibers. Furthermore, the proportion of ragged red fibers was positively correlated with the mean power frequency of the trapezius electromyogram (EMG) during an endurance-type test using an isokinetic dynamometer. Such a frequency shift of the EMG signal is indicative of muscle fatigue. Thus, these investigators were able to relate muscle morphological changes to positive physical examination findings and functional movement deficits.

In a further attempt to relate exercise performance and myalgia in female cleaners with WMSD, Larsson, Björk, Elert, and Gerdle (2000) demonstrated that while cleaners were stronger than age-matched controls, cleaners with trapezius myalgia had a lower level of endurance and a higher degree of perceived fatigue following a fatiguing shoulder flexion isokinetic exercise protocol. Of further note was the decreased ability of cleaners, both with and without myalgia, to relax the trapezius during the passive portion (i.e., shoulder extension phase) of the exercise protocol. While this EMG finding was also partly related to advancing age in the cleaning group, when taken together with the histological and clinical findings it indicates an abnormality in muscular oxidative metabolism among these women with chronic, occupation-related trapezius loading.

One of the limitations of studying workers with myalgia is the difficulty in determining the causality of their tissue and behavioral responses. Presumably, the initiating injury stimulus is long since past, and the condition of the tissues and the motor control system has been substantially altered from the preinjury state. There-

fore, it is impossible to conclude whether histochemical changes cause or follow the physiological mechanisms leading to the patient's current clinical presentation. Such uncertainty makes intervention planning, particularly prevention, difficult at best. The animal models discussed earlier have helped enormously to determine the early development of repetitive motion disorders.

Acute Low-Force Repetitive Exercise

Recently, investigators have begun to develop studies in humans that allow confirmation of some of the physiological effects of acute, low-force repetitive exercise. Such studies are possible with the use of microdialysis technique, in which small, minimally invasive catheters of semipermeable membranes are inserted into the muscle ECM during activity. The researcher then samples dialysate at appropriate time intervals in order to follow the metabolic changes in the muscle tissue.

Using microdialysis technique in healthy subjects and in women with chronic work-related trapezius myalgia, Rosendal, Blangsted, and colleagues (2004) and Rosendal, Sogaard, and colleagues (2004) have shown that highly repetitive, low-force arm movements performed for 20 min cause increases in interstitial muscle lactate, potassium, pyruvate, and IL-6. Increased lactate is indicative of an increase in anaerobic metabolism, or glycolysis. The authors concluded that the rise in anaerobic metabolism may have been caused by decreased local blood flow, inhomogeneous muscle activation, or both (Rosendal, Blangsted et al. 2004). Interstitial potassium accumulation plays a role in the regulation of blood flow, development of muscle fatigue, and sensation of pain (Rosendal, Blangsted et al. 2004). The cytokine IL-6 has pleiotropic (i.e., both pro- and anti-inflammatory) effects and has been implicated as one factor that causes exercise-induced enhancement of the immune system in low-grade inflammatory conditions (Starkie et al. 2003). It may also work in a hormonal fashion to inhibit glycogen synthase activity and facilitate glycogen phosphorylase activity, thereby increasing muscle energy supply during exercise (Kanemaki et al. 1998). Interleukin-6 also induces lipolysis (Lyngso et al. 2002), and it is upregulated in persistent pain syndromes (Winkelstein 2004). Therefore, it has immunological, neurological, and metabolic regulatory effects in muscle tissue. Women with trapezius myalgia had higher levels of interstitial glutamate and serotonin than healthy controls before exercise, which correlated with muscle pain intensity and pressure pain threshold; and glutamate increased in both groups with exercise (Rosendal, Larsson et al. 2004). These substances both act to increase the sensation of pain (Babenko et al. 1999; Zimmermann and Herdegen 1996).

In this short-term protocol with low exercise intensity, no changes in serum concentration in these metabolites or cytokines were observed. This is not surprising considering that in our rat model of low-force, repetitive reaching and grasping, tissue levels of inflammatory mediators, including cytokines, increased gradually over a period of weeks and preceded increases in proinflammatory cytokines in serum (Barr et al. 2000; Barbe et al. 2003; Barr and Barbe 2004). In another study using more intensive exercise (40% maximum voluntary contraction) of the wrist extensors for only 10 min, serum levels of IL-6 and IL-1 receptor antagonist increased (Nemet et al. 2002). Hence, an exercise-induced systemic inflammatory response has been demonstrated in humans.

In a study recently completed in our lab, we examined the serum of patients with WMSD of less than three months' duration for the proinflammatory markers TNF-α, IL-1β, IL-6, and C-reactive protein (CRP). In these early-onset cases, severity of symptoms and physical examination findings were positively correlated with TNF-α, IL-1β, and CRP (figure 12.9; Carp et al. 2007). Interleukin-6 showed a more complex relationship, with elevation in mildly and severely affected patients but not in moderately affected patients. This finding reflects the multiple and sometimes competing roles of this cytokine.

In summary, the human studies just discussed provide evidence that the performance of maximal eccentric activation tasks, low-intensity repetitive motion tasks, and other work tasks leads to muscle injury, inflammation, and repair. In the next section we describe some possible approaches to intervention for the management of WMSD as suggested by this research.

Potential Interventions

There is increasing awareness of the need to understand treatment principles for WMSD. Injury-induced release of proinflammatory cytokines can be addressed by a number of clinical interventions. Use of antagonists to specific cytokines, such as inhibitors of TNF-α, might prove useful in severe cases of WMSD. However, this type of drug would be effective only if administered during the inflammatory stage of the disorder. Blood tests for the presence of elevated serum levels of inflammatory cytokines could serve as indicators of a systemic inflammatory process. Unfortunately, a TNF-α inhibitor would not inhibit functionally redundant cytokines such as IL-1 and thus may be of limited use. This treatment regimen has yet to be tested in early-onset WMSDs.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are often taken by workers to treat pain as it arises during a work week and are also often prescribed at the time of treatment if pain is present. However, the available scientific data do not support their use. Recent studies have suggested that although NSAIDs decrease the inflammatory response (number of inflammatory cells), they also may delay the recovery process and rate of muscle fiber regeneration. In animal models

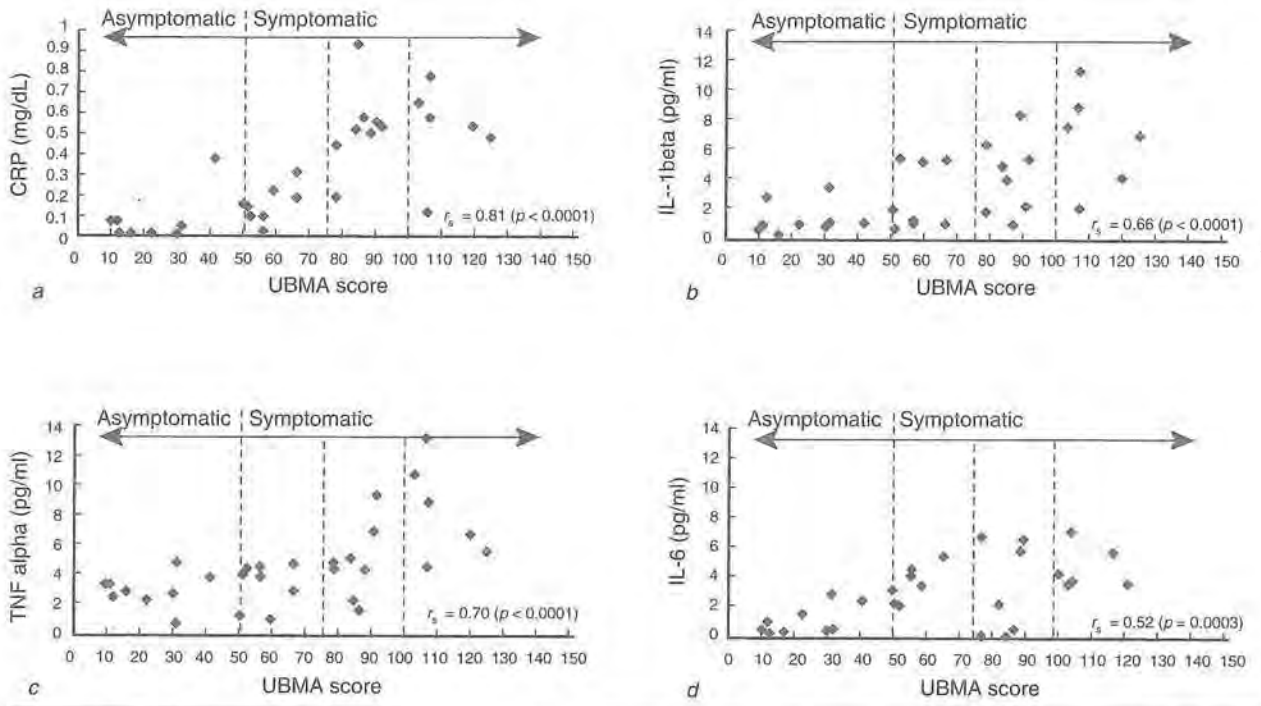

Figure 12.9 Inflammatory biomarker concentrations versus upper body musculoskeletal assessment (UBMA) scores for all symptomatic (n = 22) and asymptomatic (n = 9) subjects showing Spearman's rank correlation coefficients (r_s). *(a)* C-reactive protein (CRP); *(b)* interleukin-1β (IL-1 beta); *(c)* tumor necrosis factor α (TNF alpha); and *(d)* interleukin-6 (IL-6).

of experimental strain, administration of the NSAIDs piroxicam (Feldene), flurbiprofen, or diclofenac beginning immediately postinjury was initially beneficial (Almekinders and Gilbert 1986; Lapointe et al. 2002; Mishra et al. 1995). A few days postinjury, treated rats showed improved contractile functions, significantly less edema, and decreased levels of immune cells and muscle enzymes in the injured areas compared to untreated or placebo-treated injured rats. Unfortunately, continued administration of the NSAIDs did not maintain the improved contractile function, but instead resulted in a decline compared to values in untreated injured rats. Continued administration of the NSAIDs also resulted in delayed resolution of the macrophage response (greater number of macrophages) and delayed myofiber regeneration compared to what occurred in untreated injured rats. Thus, a generalized repression of inflammation appears to delay regenerative responses, apparently by repressing clearance of damaged myofibers by macrophages and perhaps their secretion of proliferative growth factors that would lead to repair and a regain of strength.

Treatments for injury-induced edema such as pulsed ultrasound or ice would be useful only if workers were instructed to self-administer or otherwise access them immediately, which is not typical in the workplace. Workers generally seek medical attention long after the initial swelling phase has passed.

Summary

All of the findings in animal and human experiments on local and systemic increases in metabolites and cytokines lend credence to the hypothesis that localized tissue-level responses to exercise loading lead to the resolution of any injury through normal repair processes as long as the initiating stimulus is removed. The findings also show that low-intensity exercise can cause injuries to muscle through mechanical disruption, hypoxia, or by-products of metabolism. Once injury occurs, an immune response is initiated. In cases in which the injury stimulus persists, this immune response is amplified and perpetuated until its mediators are distributed throughout the circulatory system. Such circulatory distribution may cause tissue effects in distant anatomical sites and may have psychoneuroimmunological effects on mood and behavior. Furthermore, if task intensity is high enough, the normal tissue repair process may be interrupted to the extent that permanent tissue changes occur, thereby rendering tissues more susceptible to future injury even at previously innocuous levels of task intensity. Obviously, this vicious cycle of injury, inflammation, scarring, and behavioral dysfunction should be avoided.

Skeletal Muscle Damage and Repair

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