Perspective

Pathophysiological Tissue Changes Associated With Repetitive Movement: A Review of the Evidence

Work-related musculoskeletal disorders (WMSDs) represent approximately one third of workers' compensation costs in US private industry, yet estimates of acceptable exposure levels for forceful and repetitive tasks are imprecise, in part, due to lack of measures of tissue injury in humans. In this review, the authors discuss the scope of upper-extremity WMSDs, the relationship between repetition rate and forcefulness of reaching tasks and WMSDs, cellular responses to injury in vivo and in vitro, and animal injury models of repetitive, forceful tasks. The authors describe a model using albino rats and present evidence related to tissue injury and inflammation due to a highly repetitive reaching task. A conceptual schematic for WMSD development and suggestions for further research are presented. Animal models can enhance our ability to predict risk and to manage WMSDs in humans because such models permit the direct observation of exposed tissues as well as motor behavior. [Barr AE, Barbe MF. Pathophysiological tissue changes associated with repetitive movement: a review of the evidence. *Phys Ther.* 2002;82:173–187.]

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What are the risk factors associated with work-related musculoskeletal disorders?

Work-related musculoskeletal disorders (WMSDs) of the upper extremity (UE) account for a small, but significant, proportion of injuries in US private industry and may contribute to high medical costs and long-term disability. A recent review of over 600 articles on this subject by the US National Institute of Occupational Safety and Health (NIOSH) concluded that repetitive motions, particularly in combination with high force or awkward postures, increase the risk of developing WMSDs.[1] In recognition of the seriousness of this occupational health problem, the US Occupational Safety and Health Administration (OSHA) developed guidelines for workplace ergonomic programs, which received congressional and presidential approval in the final weeks of the Clinton administration.[2]

In March 2001, however, the US Congress repealed the OSHA final Ergonomics Program Rule. Although the future of government regulation of ergonomic risk factors and WMSDs is uncertain, the basic program elements outlined in the OSHA Ergonomics Program Rule echo those recommended by NIOSH,[3] the National Safety Council,[4] and many private companies.[5–7] Among these program elements is job hazard analysis and control, which includes reduction of biomechanical risk factors such as repetition rate and forcefulness of exertions. In addition, OSHA explicitly recognized the role of physical therapists in the management of employees with WMSDs. Among these responsibilities is the assessment of an employee's readiness to return to his or her job duties. In preparation for the next iteration of proposed ergonomics regulation in the US workplace, some employers seeking the professional guidance of health care professionals and ergonomists are asking the question, "How many repetitions and how much force are safe for my employees?"

The NIOSH, through its research programs, has developed a lifting equation to assist employers in determining the maximally safe limits to manual material handling for individual employees performing specific lifting tasks,[8] and this equation has been validated in a cross-sectional study.[9] To date, no such equation or quantitative guide is available for hand- and UE-intensive tasks. This lack of an easily used quantitative guide for the UE stems, in part, from the fact that the effects of repetition rate and force on the UE in particular and the musculoskeletal system as a whole are incompletely understood. This lack of understanding is problematic given that employers may want to make adjustments to workplace practices for affected workers. Furthermore, it is likely that business groups will continue to challenge future OSHA ergonomics rules based on this lack of precise exposure-response data. The scientific and health care communities, in our view, should provide direct evidence of tissue injury to support the epidemiological evidence linking physical risk factors in the workplace to the development and exacerbation of musculoskeletal disorders. More research is needed to describe the pathophysiological responses of tissues to UE-intensive tasks and then to establish clear criteria for their prevention and management. The former goal may best be accomplished through the study of animal models of repetitive movement tasks because the analysis of tissue specimens is feasible in animals.

The objectives of our review are (1) to characterize the scope of UE WMSDs based on recent epidemiologic and clinical research, (2) to discuss recent research regarding the relationship between repetition rate and forcefulness of reaching movements and WMSDs in humans, (3) to discuss cellular responses to injury in both in vivo and in vitro experimental models, and (4) to discuss recent findings from animal injury models of repetitive or forceful tasks. A conceptual framework for the development of WMSDs in general will be proposed. Areas in need of further research will be identified, with an

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emphasis on animal models of UE WMSDs. The use of such models for future studies of the response of injured tissues to therapeutic interventions will make important contributions to physical therapy practice in occupational health care settings. We hope that this review will assist investigators in identifying key characteristics of such models and in selecting tissues and therapeutic outcomes for future study.

Scope of Upper-Extremity WMSDs

Epidemiological Evidence

The US Bureau of Labor Statistics survey from 1994 estimated that of the more than 2.25 million injuries and illnesses in US private industry resulting in lost workdays, about 332,000 were attributed to repetitive motion.[10] Although the number of occupational injuries and illnesses due to repetitive motion involving days away from work in the US has declined steadily from its peak in 1994, there were still about 247,000 cases reported in 1999 out of the 2.75 million lost workday injuries and illnesses in US private industry during that year.[11] These injuries continue to pose a substantial source of worker pain and discomfort as well as potential long-term disability and high economic toll.

Injuries of the wrist and hand constitute the majority of repetitive motion injuries of the upper limb and are also the most disabling and costly. According to a recent study of approximately 186,000 federal workers during the period from 1993 to 1994, for example, carpal tunnel syndrome (CTS) accounted for 93% of all mononeuritis claims and for 67% of all direct medical costs, with an average of $2,948 per claim.[12] Brogmus et al[13] examined the Liberty Mutual Insurance Company workers' compensation database, which contains data on a subset of US private industry workers' compensation claims. They found that the incidence of work-related musculoskeletal and nerve entrapment syndromes of the upper limb increased from less than 0.5% of all injuries and illnesses in 1986 to more than 2.5% of all injuries and illnesses in 1993. Upper-extremity WMSD claims for computer-related injuries increased from 1.6% of all UE WMSD claims in 1986 to 14.6% of all such claims in 1993.[14] Carpal tunnel syndrome was second only to forearm muscle strain injuries among computer-related WMSDs.[14] If the treatment for CTS requires surgery, this disorder can result in direct medical costs on the order of $10,000 per patient and may lead to prolonged worker absenteeism and permanent disability.

The term *work-related musculoskeletal disorder* has been defined by OSHA as a disorder of the muscles, nerves, tendons, ligaments, joints, cartilage, blood vessels, or spinal disks in the neck, shoulder, elbow, forearm, wrist, hand, abdomen (hernia only), back, knee, ankle, and foot associated with exposure to risk factors.[2] According to OSHA, these disorders may include muscle strains and tears, ligament sprains, joint and tendon inflammation, pinched nerves, spinal disk degeneration, and medical conditions such as low back pain, tension neck syndrome, carpal tunnel syndrome, rotator cuff syndrome, DeQuervain syndrome, trigger finger, tarsal tunnel syndrome, sciatica, epicondylitis, tendinitis, Raynaud phenomenon, hand-arm vibration syndrome, carpet layer's knee, and herniated spinal disk.[2] Data from epidemiological and field studies suggest that there is a relationship between the onset and severity of WMSD and the performance of highly repetitive or forceful work tasks, particularly in harsh (ie, cold or vibrating) environments.[1,15–24]

Common WMSD Diagnoses and Their Etiologies

Among jobs requiring repetitive movements of the upper limb, CTS is the most common work-related neuritis.[25–28] Because the median nerve passes through the carpal tunnel along with the long finger and thumb flexors, it is susceptible to mechanical compression or friction by the tendons themselves. Positions and movements of extreme wrist flexion, particularly in conjunction with non-neutral forearm pronation-supination, contribute to increases in carpal tunnel pressure and tensile or compressive loading of the median nerve.[29–39] This increase in pressure within the carpal tunnel may occlude blood supply, resulting in ischemic damage to both the tendons and the median nerve.[40–42]

Anoxia damages the endothelial lining of venules and capillaries, increasing their permeability and resulting in localized edema. The edema can lead to an influx of monocytes, and this influx of monocytes can induce the proliferation of fibroblasts and synoviocytes in synovial tissues, which deposit collagen.[43,44] If this collagen deposition is excessive, it may directly contribute to compression of the median nerve.[45] Other physical risk factors, such as vibration from hand-held tools, may contribute to the development of CTS.[22,46] Carpal tunnel syndrome is associated with deficits in sensation along the median nerve distribution, weakness of the thenar muscles innervated by the median nerve, hand and wrist pain, and long-term disability, including decreased endurance as measured by the rate of repetitive pinching as well as weakness and clumsiness of grasping ability.[47,48]

Musculoskeletal injuries associated with WMSD include tendinitis, tenosynovitis, ganglionic cysts, focal dystonia, fibromyalgia, myositis, bursitis, osteoarthritis, and synovitis.[49–53] Byl et al[54] were able to detect decrements in kinesthesia among patients with tendinitis associated with cumulative trauma disorder (CTD) and decrements in graphesthesia (the ability to discern and reproduce

figures drawn on the dorsum of the hand with eyes closed) and manual form perception (measured as the ability to identify and later visually match objects palpated while blindfolded) among patients with focal dystonia associated with CTD. Two research teams have reported vasodilatation and subsequent increased microcirculation to affected muscles among patients with CTD-related myositis.[55–57]

Vascular and neurovascular disorders such as Raynaud disease or reflex sympathetic dystrophy (RSD) have also been associated with WMSDs. Reflex sympathetic dystrophy has been associated with the use of hand tools that vibrate, particularly in cool working environments.[49,50] Hansford et al[58] studied workers in the suture-manufacturing industry, workers who performed repetitive upper-limb movements. They demonstrated decreased circulation in the radial and ulnar arteries at the wrist after only 1.5 hours of work. Pritchard el al[59] later found vasoconstriction of the radial arteries in workers with complaints of diffuse forearm pain associated with repetitive work. These findings suggest that repeated movements may impair circulation, with the potential for causing ischemic injury to musculoskeletal tissues and peripheral nerves.

Relationship Between Repetition-Force and WMSDs

Psychophysical Estimates of Repetition-Force Exposure

Although the localized responses of tissues to mechanical or ischemic injury are well documented, there is still considerable doubt as to the exposure-response relationship between the repetitiveness and forcefulness of a task and the onset of pathophysiology. Several researchers have attempted to establish criteria for maximum acceptable forces and movements for hand tasks based on psychophysical outcomes. Snook et al[60,61] tested female subjects who performed repetitive, forceful wrist flexion and extension or radial and ulnar deviation tasks for 7 hours per day over a period of 3 weeks. Based on subjects' symptoms, the maximum acceptable forces for a power grip task performed at a rate of 15 motions per minute were estimated for women to be 26 N (approximately 5% body weight [BW]) for wrist flexion, 15 N (approximately 3% BW) for wrist extension, and 14 N (approximately 2.5% BW) for wrist ulnar deviation. There was a decrease in maximum acceptable torque with increasing hours in the day and days of exposure in the week, with a concomitant increase in symptom and error rates as well as tactile sensitivity.

Lin and Radwin[62] used psychophysical ratings of perceived exertion (RPEs) collected in their laboratory, as well as data published by other researchers,[61,63,64] to develop a frequency-weighted filter to estimate discomfort from continuous biomechanical measurements. The resulting model showed that wrist flexion angle, force, and repetition rate during a wrist flexion task using a power grip contributed to discomfort ratings. Although Lin and Radwin did not consider duration of exposure longer than 1 hour, they confirmed the influence of repetition rate and force as risk factors for developing perceived discomfort in occupational hand-intensive tasks. Presumably, performance of such tasks for periods greater than 1 hour would only increase worker discomfort, an eventuality that has implications for activities performed throughout a typical 6- to 8-hour work shift.

Grant et al[65] demonstrated relationships between certain electromyographic (EMG) measurements of upper-limb muscles and of RPE and grip force. Although the number and weight of the EMG and RPE variables depended on the specific task in question, grip force could be predicted to a moderate degree (r^2=.52–.63). Grant et al, therefore, helped to establish a relationship between muscle physiology, worker perception, and functional activity.

Biomechanical Estimates of Repetition-Force

In their classic study, Silverstein et al[24] performed job analyses of industrial workers that included videotaping job task cycles (ie, the basic sequence of movements required to perform the task goal). Based on these measurements, the authors defined high repetition rate as less than 30 seconds per cycle and low repetition rate as greater than 30 seconds per cycle. Surface EMG recordings of the forearm flexors were obtained during grip exertions of known force. Using these reference EMG recordings, estimates of hand force were made from EMG recordings collected during the performance of job cycles and were used to define low force as hand force below 1 kg and high force as hand force above 4 kg. The authors reported prevalence ratios for WMSDs of 3.6 for high-repetition–low-force tasks, 4.9 for low-repetition–high-force tasks, and 30.3 for high-repetition–high-force tasks. This and later work strongly suggest that the interactive effects of repetition and force are more than additive in contributing to the risk for development of WMSDs.[19,23,28]

Given that force is a continuous variable, defining discrete levels of force that are relevant to the occupational setting in which workers are at risk for WMSDs may be crucial to investigations of this injury process. Many authors have defined force levels based on estimates of force needed for components of tasks, observations of workers, or direct measurements. Table 1 summarizes a number of such studies[19,24,28,36,65–68] and the resulting force level definitions for hand-intensive work tasks. These data show that, despite the differences in methods of force estimation, there is a consensus that an exertion

Table 1.
Summary of Studies Investigating Repetition-Force Levels of Hazardous Hand-Intensive Occupational Tasks[a]

Reference No.	Study Type	Sample	Method of Force Estimation	Force Levels	Findings
66	Cross-sectional	N=161	Task-based with subsample of direct measurements	High>100 N	OR=1.11 for wrist pain at high force level
36	Experimental	N=12 UE (cadaver)	Manipulated according to Armstrong et al, 1982	Range of applied loads: 23, 46, 65, 80 N	Nonlinear, monotonically increasing relationship between applied load and finger flexor tendon strain, with creep evident within a physiological load range
65	Experimental	15 males	Direct measurement of grip force with different object masses	Grip force categories: Lt≈14% MVC grip Med≈23% MVC grip Hvy≈31% MVC grip	RPE (Borg) reflects grip load, which is in turn related to object mass (Lt=0.5 kg, Med=1.1 kg, Hvy=2.3 kg)
67	Statistical model	Literature data	Stress-strength interference model	High>100 N	Probability of tendon failure increases above high force level
19	Cross-sectional	N=230	Weight of object and estimated maximum strength of workers	Neg≤15% MVC Lt=16%–30% MVC Md=31%–50% MVC Hvy=51%–75% MVC VHvy>75% MVC	Force was most highly weighted risk factor in regression analysis for UE WMSD morbidity
68	Clinical intervention	N=33	Electromyographic biofeedback of upper trapezius muscle	Critical value: 10% MVC	Musculoskeletal symptoms decreased if upper trapezius muscle activation stayed below critical value
24	Cross-sectional	N=574	Direct measurement of subsample	Avg low=3 kg Avg high=12.7kg	Plant adjusted OR for hand and wrist WMD: LOF.LOR=10 HIF.LOR=4.9 LOF.HIR=3.6* HIF.HIR=30.3
28	Cross-sectional	N=652	Weight of tools/materials	High>40 N grasp Low<10 N grasp	OR for hand and wrist tendinitis: LOF.LOR=1 HIF.LOR=6.1 LOF.HIR=3.3 HIF.HIR=29.4

[a] OR=odds ratio, LOF=low force, LOR=low repetition, HIF=high force, HIR=high repetition, RPE=Borg scale for rating of perceived exertion, MVC=maximal voluntary contraction, Avg=average, Lt=light, Med=medium, Hvy=heavy, VHvy=very heavy, Neg=negative, WMSD=work-related musculoskeletal disorder, UE=upper extremity. Asterisk indicates lack of statistical significance.

requiring less than 15% of maximum grip force can be considered negligible to low and exertions requiring greater than 50% of maximum grip force can be considered high. This leaves the range of 16% to 49% of maximum grip force as a moderate force range for gripping or grasping tasks.

Direct Observation of Tissues Exposed to Repetitive or Forceful Tasks

Although researchers in studies such as those already cited in this review have attempted to quantify and relate perceived exertion and WMSD symptoms, their use of noninvasive methods to estimate worker performance or risk creates limitations in studying pathophysiology in human subjects. Investigators are unable to easily relate psychophysical and biomechanical measures with pathophysiological changes. Using an invasive approach, Dennet and Fry[69] performed open biopsies on affected first dorsal interosseous muscles in patients with painful chronic overuse syndrome and found histological and ultrastructural changes in muscle fibers consistent with denervation or ischemic loss of type II muscle fibers and hypertrophy of type I fibers. Larsson et al[70] showed the presence of cellular pathology related to mitochondrial dysfunction in trapezius muscle biopsies from assembly-line workers with localized chronic myalgia of the trapezius muscle related to static shoulder postures during precision manual tasks. The observed changes were consistent with localized hypoxia and were correlated with reduction in muscle blood flow.

The number of such tissue studies in humans is very small because of the invasiveness of tissue analysis techniques. In addition, it is impossible in these studies to

control (or even accurately measure) the amount of repetitive activities performed by a person with a WMSD. Consequently, many questions about the interaction of repetition rate and force and the precise pathophysiological changes of the tissues remain unanswered. The extent to which such behaviors impair the motor control system and lead to functional limitations and chronic disability are just beginning to be recognized. This lack of knowledge is, in part, responsible for the persistent controversy in the United States and other industrialized nations surrounding the degree to which musculoskeletal disorders are the outcome of repetitive occupational tasks as opposed to the usual and expected consequences of typical activities of daily life. In addition, individual predisposing factors, such as comorbid medical conditions, may contribute to the onset and severity of WMSD. Thus, regulatory progress to prevent and manage these disorders, despite the strong epidemiological evidence for their existence, continues to be impeded.

A more precise understanding of the effects of repetitive and forceful tasks on tissues may help to guide therapeutic strategies for preventive and early care of affected individuals, rehabilitation approaches for subacute and chronic conditions associated with WMSD, and prevention of chronic disability. Given the impediments to observing the tissues directly in humans in either the workplace or health care settings, animal injury models provide an alternative means of elucidating the exposure-response relationship between repetition-force and WMSDs.

Cellular Indicators of Injury

There are expected cellular and biomechanical changes to tissues that researchers may use to study in animal injury models. Structural damage to most tissues results in the proliferation of progenitor cells of that tissue.[43,45,71] A simultaneous infiltration of lymphocytes, macrophages, and other phagocytic cells occurs in response to a diffusion of intracellular factors through damaged plasma membranes.[72,73] The combination of these proliferative and infiltrative processes can lead to tissue changes over time. For example, mechanical injury to muscle fibers results in disruptions of the sarcolemma and sarcomere, which causes leakage of cellular components into the extracellular matrix and diffusion of serum components into and around the myofibers.[74–76] These alterations of the extracellular matrix can lead to tissue regeneration or scarring.[74,75] Repeated muscle injury results in expansion of extracellular matrix and collagen deposition around the myofibers (ie, fibrosis) and fiber necrosis. Direct damage to tendons and ligaments causes a similar process of fibroblast proliferation, which leads to fibrosis and collagen dysplasia.[77–81]

When cells experience mechanical or metabolic stresses, whether acute or chronic, they react by increasing the production of a family of proteins called heat shock proteins (HSPs).[82,83] These proteins are produced following inflammation, infection, hyperthermia, ischemia, nerve crush or transection, neural degenerative diseases, or exposure to various toxins.[84,85] A variety of cell types produce these proteins in response to injury, including neurons, glia, fibroblasts, and muscle cells. These proteins have been shown to have a protective role in the cell.[86] During periods of cellular stress or injury, the inducible HSP-70/72 increases to recognize and restore denatured proteins to their native state.[87,88] The presence of these stress proteins in peripheral tissues following a repetitive motion task would indicate that a repair process has begun, resulting from the accumulation of denatured proteins.[89,90] Various disrupters of cellular proteins that may occur in WMSDs include ischemia, microtears in the cell membranes, or the release of cytotoxic free radicals from damaged cells. The study of the induction of these proteins in response to repetitive movements could lead to clinical interventions that may halt the progression of chronic WMSDs and disability.

Primary tissue damage also results in a cellular release of cytokines, which are mediators of inflammation, cell proliferation, cell migration, and regeneration.[91–93] Many peripheral tissue cell types, including fibroblasts, myocytes, and endothelial cells, respond to damage by upregulating a number of proinflammatory proteins, including interleukin-1 (IL-1), IL-6, tumor necrosis factor alpha (TNFα), and prostaglandin E2.[91,93–95] Cytokines released during acute inflammation (eg, IL-1α, IL-1β, TNFα) mediate the proliferation and maturation of macrophages and other mononuclear cells as well as fibroblasts.[96–99] Activated macrophages and other mononuclear cells then produce even more cytokines, such as IL-1, IL-6, and IL-11, that further stimulate inflammation.[71,98,100,101] Interleukin-1 enhances the expression of COX2, a proinflammatory enzyme with an important role in the synthesis of prostanoids, such as prostaglandin E2. Interleukin-1and TNFα also serve as potent stimulators of osteoclast activity.[102–106] The phagocytic action of the activated inflammatory cells and osteoclasts can result in direct tissue damage. Thus, a vicious cycle of tissue damage can be initiated, leading to chronic inflammation.[96] We hypothesize that in repetitive tasks, this injury cycle is prolonged and thus amplified by continued task exposure. This hypothesis, among others, can be tested in animal models of repetitive movement disorders.

Animal Models of Repetitive Movement Disorders

Although many epidemiological and clinical studies of human subjects have demonstrated a link between repet-

Table 2.
Musculoskeletal Changes in the Pathophysiology of Cumulative Trauma Injury

	Species	Reference No.
Tendon and tendosynovial changes		
Tendinitis, tenosynovitis	Human; guinea pig	52; 53
↓ kinesthesia	Human	54
Microdamage due to tension, compression, and shear	Human	36
↑ production of collagen and rearrangement of fibers	Human; rabbit	52, 81; 78
↑ fibroblasts	Rabbit	45
Tendon and tendon-axon adhesions	Human; rabbit	36; 45
↑ protaglandin E2 and leukotriene B4	Human	92, 94
Synovitis, destruction of synovial membranes	Human	37, 50
↑ inflammatory cells and cytokines	Rabbit; rat	78, 108; 51
Connective tissue thickens and becomes fibrous	Rabbit; rat	78, 108; 45, 74
Altered expression of matrix components and proinflammatory cytokines	Rabbit, rat	78, 108; 51
Vascular proliferation around tendon and in synovium	Rabbit	45
Flexor retinaculum changes		
↑ vimentin, ↓ tubulin	Human	80
Fibroblasts converted to myofibroblasts	Human	80, 126
Collagen dysplasia	Human	81
Muscle changes		
↑ inflammatory cells	Rat	51
↑ heat shock protein	Rat	51
↓ grip strength	Human	47, 48
↑ number of muscle fibers	Human	69
Hypertrophy of muscle fibers	Human; rat	69; 109
Mitochondrial changes in type II fibers	Human	70
↑ blood flow in general forelimb area	Human	55–57
Loose connective tissue changes		
↑ inflammatory cells	Rat	51
↑ heat shock protein	Rat	51
Bone and cartilage changes		
Intervertebral disk protrusion/prolapse	Rat	107
Vertebral growth plate thickness defects	Rat	107
Chondrocyte clumping/disorganization	Rat	107

itive, forceful motor tasks and the development of localized musculoskeletal and peripheral nerve injury, a clear relationship between the amount of repetitive activities and the pathophysiological findings has not been established. Animal models of both repetitive movements as well as other mechanisms of injury have provided some valuable information in this regard. Those studies that represent a cross-section of the literature or that make a unique contribution to this review are discussed in detail in the paragraphs that follow. A more extensive list of such studies* is summarized briefly in Tables 2 and 3.

Involuntary Movement Models

Repetitive passive flexion and extension of the tails of rats at 25 Hz for 2 hours per day, 6 days per week, for 8 weeks have resulted in histological changes in tail vertebrae.[107] Intervertebral disk and bone changes included disk protrusion into the vertebral end plate, disk prolapses without protrusion at the disk-end plate interface, growth plate dislocation and thickness variation, and trabecular irregularity in the vicinity of disorganized growth plate regions. Cartilage changes included clumping of chondrocytes and decreases in both number and organization of chondrocyte columns. The histological findings were not accompanied by any symptoms or behavioral indicators of discomfort or functional loss, which demonstrates that skeletal tissues, as well as soft tissues and nerves, may be sensitive to repetitive, submaximal loading and that tissue disruption may precede symptoms and functional impairments.

A model of repetitive movement injury using the scratch reflex movement of the rabbit hind limb resulted in histological changes consistent with localized Achilles tendon inflammation after a training period of 6 to 8 weeks.[78] High and low load-repetition protocols were followed for 1 to 2 hours per day, 3 days per week. Although gross morphological changes were not observed in any of the loaded tendon specimens, inflammatory cells and areas of hypercellularity were observed in the outer tendon after 6 and 8 weeks regardless of loading protocol. Expression of the inflammatory mediators IL-1β and TNFα was also increased.[108] These findings suggest an injury response to submaximal repetitive loading that is consistent with the nature of the complaints of patients with WMSDs such as dull, burning aches associated with localized inflammation. This work also illustrates the usefulness of animal models in which amount of repetitive activity can be controlled and the response of tissues can be observed directly.

Repeated forced-lengthening, or stretch, has speed-specific effects on rat soleus muscle.[74,109] In these studies, the soleus muscle was electrically stimulated while repeated stretching through forced ankle plantar flexion and dorsiflexion was carried out at slow and fast speeds every other day for 4 weeks. Slow stretching resulted in an increase in muscle mass that was caused by muscle fiber hypertrophy. Fast stretching also resulted in

* References 17, 36, 37, 39, 40, 42, 45, 47, 48, 50–58, 69, 70, 74, 78, 80, 81, 92, 94, 107–136.

Table 3.
Neurological Changes in the Pathophysiology of Cumulative Trauma Injury[a]

	Species	Reference No.
Neuronal changes		
Excursions and strain in the median nerve	Human	36, 39
Wallerian degeneration of myelinated fibers	Guinea pig	127, 128
Prolongation of distal motor latency	Human; guinea pig	129; 128
Slowing of median sensory NCV at wrist	Human	17, 129, 130
Cytoskeletal changes in cutaneous sensory receptors	Human	131
Perineuronal changes		
Endoneurial swelling above compression site	Guinea pig; human	53; 132
Intraneural fibrosis	Human	37, 40
↓ intraneural blood flow due to nerve compression	Human; rabbit	40, 58; 42
Glial changes		
Progressive thickening of epineurium and perineurium	Guinea pig	53
Degradation and progressive thinning of myelin	Guinea pig; human	127, 128; 132
Distortion of myelin fiber internodes	Guinea pig	53
↑ GAP 43 in Schwann cells	Rat	133
Central nervous system changes		
Psychomotor deficits	Human	47
↓ in NGF in dorsal horn	Rat	134
Degradation of hand representation in S1	Nonhuman primate	124, 125, 135, 136
↑ expression of substance P	Rat	110–113

[a] NCV=nerve conduction velocity, NGF=nerve growth factor.

an increase in muscle mass, but the reason for the increase in mass in this case was an increase in noncontractile tissues without muscle fiber hypertrophy. In addition, the fast-stretch protocol resulted in the appearance of many smaller, less mature muscle fibers, which suggests myofiber regeneration in response to muscle injury. These results illustrate the gradation of effects of forceful and repetitive movements on the muscular tissues and suggest that a threshold exists between acceptable loads and rates of loading and those that cause tissue injury. It is important for clinicians to be able to estimate how close the force and repetition requirements of a particular job are to this injury threshold.

Pain and Peripheral Nerve Injury Models

Numerous researchers have shown that chronic pain leads to neuroplastic changes in the spinal cord of rats. Chronic pain, particularly chronic intense pain, results in repeated activation or chronic stimulation of nociceptive afferents from application of capsasin or formalin or from joint inflammation.[110–112] The sustained nociceptive afferent barrage causes a release of excitatory neurotransmitters and neuropeptides such as glutamate[113] and substance P (SP). Substance P activates its receptor, neurokinin-1 (NK-1), located on dendrites of postsynaptic neurons in dorsal horn superficial laminae. Glutamate activates the N-methyl-D-aspartate (NMDA) receptors that are co-localized with NK-1. Activation of both receptors has been shown to stimulate complex cascades of intracellular events within the postsynaptic cell. One action is the release of a retrograde messenger, nitrous oxide, which stimulates an increased release of glutamate from the presynaptic cell and thus further activates NMDA receptors postsynaptically.[114] Other cascades result in alterations in genes that lead to an upregulation of receptors as well as hormones, peptides, and enzymes in the postsynaptic cell.[115] The end results are hyperalgesia and allodynia via the potentiation of the pre-existing synapse and an increase in the responsiveness of the postsynaptic cell to afferent inputs of any type.[116–118] In people with WMSDs, this is manifested as painful sensations in response to nonpainful stimuli. Such a complaint among people with chronic pain may be interpreted by clinicians as "symptom amplification," a term that connotes a psychological basis for symptoms when a pain response elicited on examination seems to exceed the intensity expected from the clinical signs.

Nerve constriction also causes neuroplastic changes, including decreases in SP in the dorsal horn, increases in NK-1 receptor in the dorsal horn, and *de novo* expression of neuropeptide Y (an excitatory neuropeptide) in the dorsal root ganglion (DRG).[117,119] Central neuroplastic-changes may occur with acute, localized inflammation and peripheral nerve compression brought about by the performance of repetitive, forceful tasks. There is evidence of activity-induced synaptic modification of central neuronal networks.[120,121] These neuroplastic changes may occur at multiple levels of the somatosensory pathways following peripheral nerve injury and CTS.[122,123] These hypotheses are as yet untested in an in vivo WMSD injury model of a voluntary repetitive movement task.

Voluntary Movement Models

Repetitive grasping movements of the upper limb and hand have been shown to induce dedifferentiation of topographical fields in the S1 (Brodman's area 3b) somatosensory cortical region in owl monkeys.[124,125] In animals that performed the task with simultaneous clos-

ing followed by opening of all digits, the somatotopic changes were consistent with other findings of surgical syndactyly and supported the idea that the central representation of digital independence is reliant on the timing of somatosensory input.[137,138] Animals using the simultaneous digit movement pattern experienced a decrement in task performance and related functional activities after 3 or 24 weeks of training that was consistent with occupational hand cramps. The results of this work suggest that neuroplasticity induced by highly constrained and repetitive behaviors may contribute to the behavioral consequences of such tasks irrespective of localized injury. Histological analysis of hand and wrist tissues by these investigators using hematoxylin and eosin staining yielded no evidence of acute, localized inflammation. This finding supports the idea that there were neurologically induced behavior changes. Based on these findings, it is arguable that maladaptive behavior in highly repetitive tasks is, in part, centrally mediated and may be unresponsive to interventions that address only localized injury.

In our laboratory, we have developed an in vivo, voluntary repetitive movement injury model in the rat that simulates an occupational paced reaching and grasping task. An example of a paced task would be repeatedly placing small objects that are traveling on a conveyor belt into a package crate. In such a job, the pace is controlled by the rate of speed of the conveyor belt, and the same reaching and grasping cycle is repeated throughout the task shift. This model allows us to observe the effects of repetition on tissues and on motor behavior. In this model, adult Sprague-Dawley (albino) rats 12 weeks of age are trained to reach into a narrow tube placed at shoulder height to retrieve small, spherical food pellets dispensed at a predetermined rate. Reach repetition rate, reach success, and gross movement behavior are recorded during task performance sessions. Several cohorts of animals have worked from 2 to 9 weeks at a target repetition rate of 4 reaches per minute for 2 hours per day, 3 days per week.

Using this model, we have shown that 2 increasingly maladaptive reach movement patterns emerged in rats trained to perform the reaching and grasping task for up to 9 weeks.[51] The scooping pattern, in which the digits were semiflexed and the pellet was dragged along the floor of the feeding tube and scooped into the mouth, was observed in 80% of trained animals by week 7. The raking pattern, in which the digits were extended and the pellet was contacted repeatedly in an inefficient raking motion until it was advanced toward the tube opening, was observed in 100% of trained animals by week 8. Heat shock protein-72-IR cells were increased over control levels in the myofibers and loose connective tissues of the lumbrical muscles by 3 weeks of training, and in the tendons and muscle bellies of the distal forelimb flexor muscles by 4 weeks. COX2-IR cells were also present in these tissues and in the radiocarpal ligaments by 6 weeks of training. These latter 2 findings suggest progressive injury to forelimb tissues.

Macrophage infiltration, as indicated by ED1 expression, was quantified in the radiocarpal ligament and the flexor muscles and associated tendons of the palms and distal forelimbs of trained animals as well as controls. The numbers of ED1-IR macrophages increased as much as 1,000 times above control levels in the muscle and tendon of forelimbs used to reach (reach limbs) from 3 to 5 weeks of task performance, with a return toward control levels by 6 weeks. The progressive increase in ED1-IR cells was also observed in contralateral, nonreach limbs, but lagged that in reach limbs by 1 week and had a twofold to threefold lower response magnitude. The IL-1β levels showed a pattern of increase similar to that of ED1-IR cells. The presence of a lower response magnitude in the nonreach limbs that lags that in the reach limbs suggests a systemic inflammatory response to a high-repetition–negligible-force reaching and grasping task. This possibility warrants further investigation, particularly in light of the sometimes vague and nonlocalized complaints of patients with WMSDs who may be affected by such widespread effects of localized task performance.

We have recently begun to explore the consequences of increased task forcefulness on peripheral tissues, behavior, and neuroplasticity. We believe such investigations are enhanced by our model of a voluntary repetitive movement paradigm. The insights into the physiological and behavioral adaptations of organisms to the adverse effects of such task demands should be even more applicable to the human condition than reflexive or other involuntary movement models.

A Conceptual Schematic for WMSDs

A summary of the pathophysiological changes arising from cumulative trauma injury, regardless of its work-relatedness, in various species and experimental paradigms is provided in Tables 2 and 3. Based on our review of the literature, a conceptual schematic for the development of WMSD resulting from the performance of a repetitive, forceful, posturally constrained movement is proposed (Figure). Noted in this figure are the points in this injury process when clinicians are most likely to intervene. This time frame for clinical intervention may be too late to reverse some of the pathophysiological and neuroplastic changes that have already taken place, which perhaps explains why chronic disability is an increasing consequence of WMSDs.

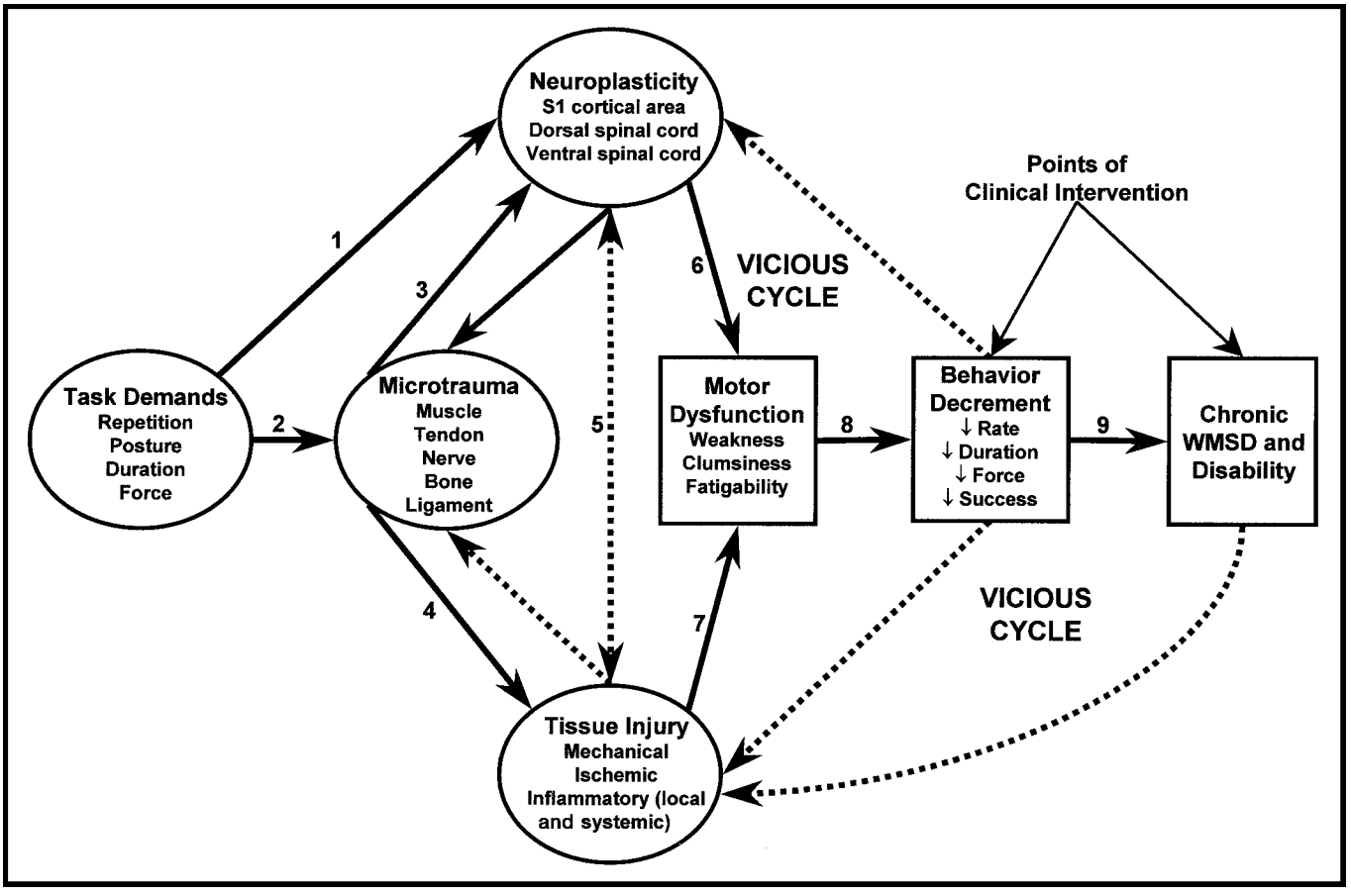

Figure.
Conceptual schematic for the development of work-related musculoskeletal disorders (WMSDs). Solid arrows indicate steps supported by recent research. Dotted arrows indicate steps requiring elucidation. Concepts enclosed by ovals represent inputs to the behavioral consequences of task-induced changes. These behavioral consequences are enclosed by rectangles. The common time points for clinical intervention are indicated by lighter arrows. The current most commonly assumed pathway to chronic WMSD and disability due to exposure to ergonomic risk factors follows the sequence indicated by arrows 2–4–7–8–9. This common pathway is strongly supported by the work of Barr et al.[51] An alternative pathway supported by the work of Byl and colleagues[124,125] for focal hand dystonia follows the sequence 1–6–8–9. Another alternative pathway for the early portion of this disease process follows the sequence 2–4–5, but future work by these authors has yet to explore this and other proposed pathways indicated by dashed lines.

Areas for Further Research

Because of the intricacy of the responses to the performance of repetitive tasks over time, a complete understanding of pathophysiological and behavioral phenomena requires an in vivo animal injury model that reasonably approximates humans. We view the essential elements of such a model to be as follows:

1. The repetitive task must be voluntary in order to engage the entire motor control system; therefore, the animal species must be trainable by standard operant-conditioning procedures.

2. The anatomy of both the musculoskeletal and nervous systems must be well described and sufficiently similar to that of humans. This would limit the potential species to mammals.

3. Investigators should be able to monitor motor behavior in terms of both target task speed and accuracy as well as other indicators of motor function such as strength and movement patterns; therefore, a species should be chosen for which the target movement has been described and test procedures have been validated.

4. Methods must be well described and supplies commercially available for immunohistochemical/biochemical analyses of the tissues of the musculoskeletal and nervous systems. In order to ensure the usefulness of any models in multiple laboratories for corroboration of findings, we should preclude the use of immunohistochemical/biochemical assays developed in specific laboratories, which is common in this field of investigation.

In our laboratory, we have recently developed such an injury model using the Sprague-Dawley (albino) rat. The literature on the training, testing, and tissue analysis of this species is rich and meets all 4 of the criteria we listed. The fact that the rat is a quadruped animal raises concerns regarding exposure amplification to the forelimb due to normal weight bearing. This variable can best be controlled through the use of control animals. The reaching behavior, anatomy, and physiology of the rat are well described. In addition, procedures for assessing all of these attributes are available in the scientific literature and, to a large extent, commercially available equipment exists to do so. This makes the use of this species attractive.

Animal models can be used to elucidate the exposure-response relationship between risk factors and the onset and severity of WMSDs. Several animal models of different species and subspecies of mammals are currently in use and show consistent results that corroborate clinical findings in humans. Thus, it would appear that despite genetic variations between species or genetic homogeneity of a particular subspecies, animal models may help to answer mechanistic questions that are inapproachable in humans. Risk factors that can be studied in animal models include repetition rate and forcefulness of exertions to perform tasks. These risk factors could be studied alone or in combination. Exposure to different levels of risk for variable work shift duration would also help to elucidate these exposure-response relationships.

The effects of therapeutic interventions could be tested in animal models. Rats would be amenable to a variety of therapeutic approaches, including, for example, the implementation of work-rest cycles, aerobic fitness programs, job rotation schemes, pharmaceutical interventions, and environmental controls. Although studies of more cortically intensive interventions would be impractical in the rat, some sensorimotor integration techniques might be feasible in this species.

Conclusion

In the *Guide to Physical Therapist Practice*,[139] the model definition of physical therapy includes examining work barriers, ergonomics, and body mechanics as well as the impairments and functional deficits associated with musculoskeletal and motor dysfunction. Physical therapists, therefore, may be called upon to identify workplace risk factors that can be modified to relieve, reduce, or prevent musculoskeletal injury. Yet, our current knowledge of the magnitude of risk given a particular level of exposure is limited by the fact that few researchers have observed the onset of tissue injury directly. The use of animal models will enhance the ability of investigators to make predictions of risks, thereby informing clinicians about more effective management of WMSDs.

Animal models permit the exploration of tissues and components of the motor control system heretofore unreported in the occupational health literature. Although we assume that the injuries sustained from repetitive, forceful work are primarily in the peripheral musculotendinous and neural tissues near the exposure site, there is increasing evidence that a systemic response may develop and that neurological reorganization may take place more centrally in the spinal cord and even in the cerebral cortex. Neuroplastic reorganization may precede the onset of motor decrements, thereby contributing to the onset of localized injury. If repetitive movements cause cortical plasticity, it is probable that spinal cord and brain-stem plasticity has also occurred, because sensory inputs to the cortex originate in the periphery. Such alterations may be more amenable than cortical regions to direct therapeutic intervention, and strategies for clinical management of WMSDs may have to include restoring and maintaining somatotopic differentiation of central nervous system representations of involved body segments and treatment of distant musculoskeletal tissues rather than simply improving the physical capacity of the tissues near the exposure site.[140] Therefore, the extent of the reversibility of such distant tissue and neuroplastic changes in the context of a repeated-movement behavioral paradigm needs to be demonstrated. An in vivo, voluntary movement model in the rat is well suited for the investigation of physical risk factors, such as repetition rate and forcefulness of exertions, and provides an opportunity to examine the interactive effects of multiple risk factors on both the motor behavior and pathophysiological consequences of repetitive movements.

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