ARTICLE

Systemic Inflammatory Mediators Contribute to Widespread Effects in Work-Related Musculoskeletal Disorders

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BARR, A.E., M.F. BARBE, and B.D. CLARK. Systemic inflammatory mediators contribute to widespread effects in work-related musculoskeletal disorders. *Exerc. Sport Sci. Rev.*, Vol. 32, No. 4, pp. 135–142, 2004. *Recent studies in a rat model have indicated that the pathophysiological mechanisms underlying development of work-related musculoskeletal disorders (WMSDs) include widespread inflammation and subsequent fibrosis at high levels of repetition and force. A systemic inflammatory component may affect tissues not directly involved in task performance, thereby contributing to widespread and puzzling symptoms that are often characteristic of patients with WMSDs.* **Key Words:** cytokines, localized inflammation, musculoskeletal injury, peripheral nerve injury, rat model, repetitive motion disorders, systemic inflammation, fibrosis

INTRODUCTION

Highly repetitive and forceful hand-intensive occupational tasks have been associated with a number of severe and chronic disorders of the musculoskeletal and neuromuscular systems, including carpal tunnel syndrome, tendinitis, and osteoarthritis. These so-called work-related musculoskeletal disorders (WMSDs) account for the majority of all occupational illnesses in the United States (4) and represent substantial economic cost. Despite ample epidemiological evidence for the role of repetition and force in the onset and progression of WMSDs (11), complete understanding of these important occupational health problems requires elucidation of the pathophysiological mechanisms of the tissue response. Of particular concern is the controversy surrounding the degree of work-relatedness of activity-induced musculoskeletal disorders. Workers may be exposed to high-risk tasks in both workplace and nonworkplace settings. Health problems or overall fitness may also affect the susceptibility of individuals to development of WMSDs. Such comorbidities cloud the debate concerning appropriate interventions for WMSDs not only because they confuse clinicians about the causal factors underlying these disorders, but also because they make it difficult for third party payers to partition costs associated with treatment and indemnity payments. One signal that health care providers or insurance adjustors may use to estimate the contribution of workplace risk factors to a WMSD case is the anatomical location of signs and symptoms in the context of the work task believed to contribute to the disorder. If a task requires heavy use of the dominant hand, for example, one would expect symptoms to be restricted to that side. Such reasoning has routinely been used to argue against the designation of bilateral carpal tunnel syndrome as a WMSD. However, in recent studies in our laboratory using a rat model of a repetitive motion disorder, we have discovered the presence of circulating pro-inflammatory cytokines as well as evidence of tissue inflammation in anatomical regions not directly associated with the performance of an intensive unilateral reaching and grasping task (1). We conclude that the presence of cytokines in the blood stream of affected animals, initiated by a unilateral upper limb task, contributes to the development of widespread and bilateral pathophysiological and behavioral changes. This hypothesis explains the presence of widespread symptoms, a central controversy in the management of WMSDs.

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REPETITIVE MOTION LEADS TO TISSUE INJURY AND INFLAMMATION

A dose-dependent injury and inflammation cycle is stimulated by the performance of highly repetitive and/or forceful reaching, grasping, and pulling by trained rats (1,3,6). Figure 1 summarizes the time course of the inflammatory response, through the immunohistochemical analysis of musculoskeletal tissues for exudate macrophages, in reach and nonreach forelimbs of trained rats. At an exposure level of eight reaches·min^{-1} and negligible force for 2 h·day^{-1}, three d·wk^{-1}, macrophages increased in number in the injured tissues, with a peak between 5 and 8 wk after the start of the task regimen (1,2,3,6). This increase in macrophages is attributed to their attraction to the injury site through chemotaxis, induced via byproducts of tissue injury (*e.g.*, collagen fragments and other cellular debris, release of free radicals by phagocytic cells, and upregulation of proinflammatory cytokines by injured cells). Reducing the exposure level to half the reach rate eliminated the injury-inflammation cycle (2). The tissues that underwent injury and inflammation included muscle, tendon, loose connective tissue, bone, and peripheral nerve (1,2,5,6). Tissues from both forelimbs (the "reach" limb that was used to perform the task as well as the contralateral "nonreach" limb) were affected.

DOES THE BILATERAL RESPONSE RESULT FROM UNILATERAL OR BILATERAL EXPOSURE?

The discovery of a bilateral inflammatory response of distal musculoskeletal and neural tissues to a unilateral repetitive motion in our rat model led us to hypothesize two causal pathways: 1) the forelimbs of our quadruped subjects were

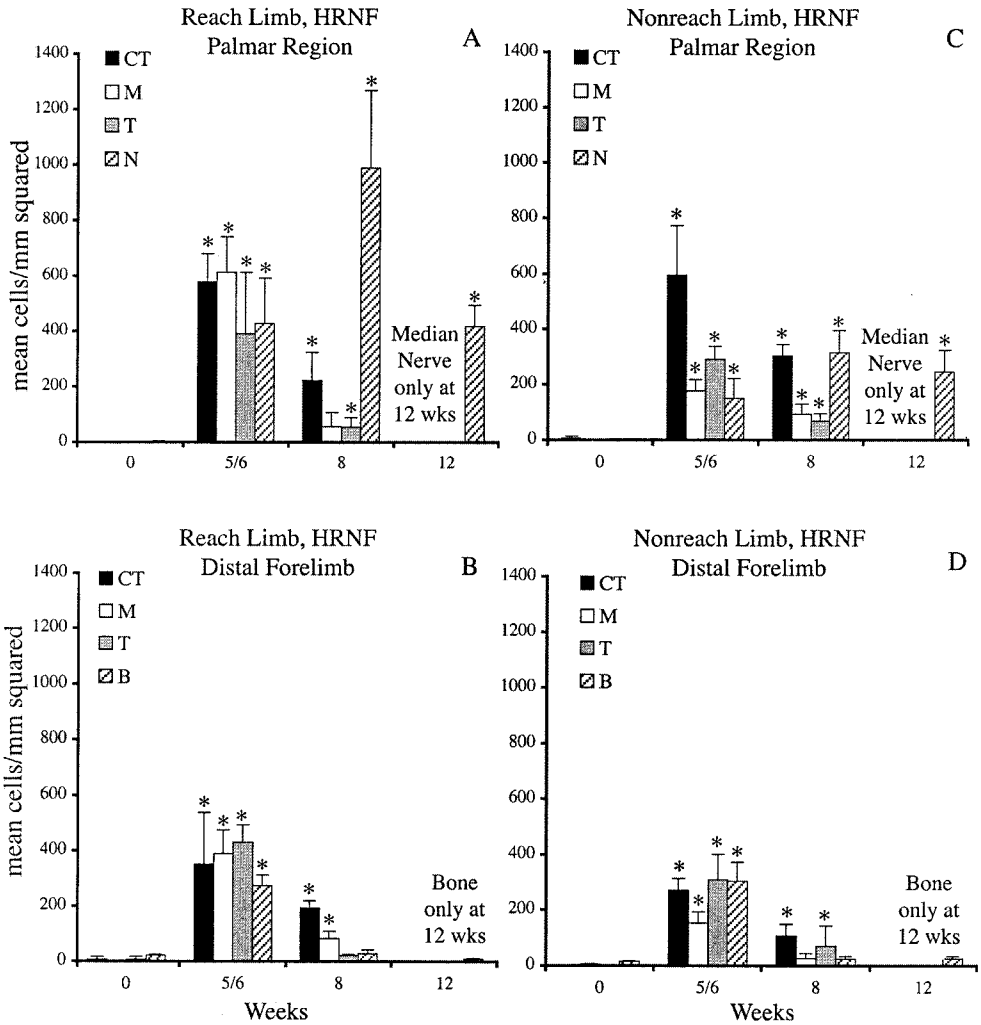

Figure 1. Average number of ED1+ (activated) macrophages + SEM, determined by bioquantitation, observed in various tissues of the palmar and distal forelimb regions of the reach and nonreach limbs of rats that performed a high-repetition, negligible-force (HRNF) reaching and grasping task for up to 12 wk. The number of macrophages peaked between 5 and 8 wk, indicating an inflammatory response, and decreased toward control numbers by 8–12 wk, indicating resolution of the inflammation. A) Palmar region, distal to the carpal tunnel, of the reach limb. B) Palmar region of the nonreach limb. C) Distal forelimb, below the elbow to above the carpal tunnel, of the reach limb. D) Distal forelimb of the nonreach limb. * $P < 0.05$ compared with 0 wk controls. CT, loose connective tissue; M, muscle; T, tendon; *N*, nerve; B, bone. [Adapted from Barbe, M.F., A.E. Barr, I. Gorzelany, M. Amin, J.P. Gaughan, and F.F. Safadi. Repetitive motion causes local injury, systemic inflammation and reach pattern decrements in rats. *J. Orthop. Res.* 21:167–176, 2003. Copyright © 2003 Orthopaedic Research Society. Used with permission.]

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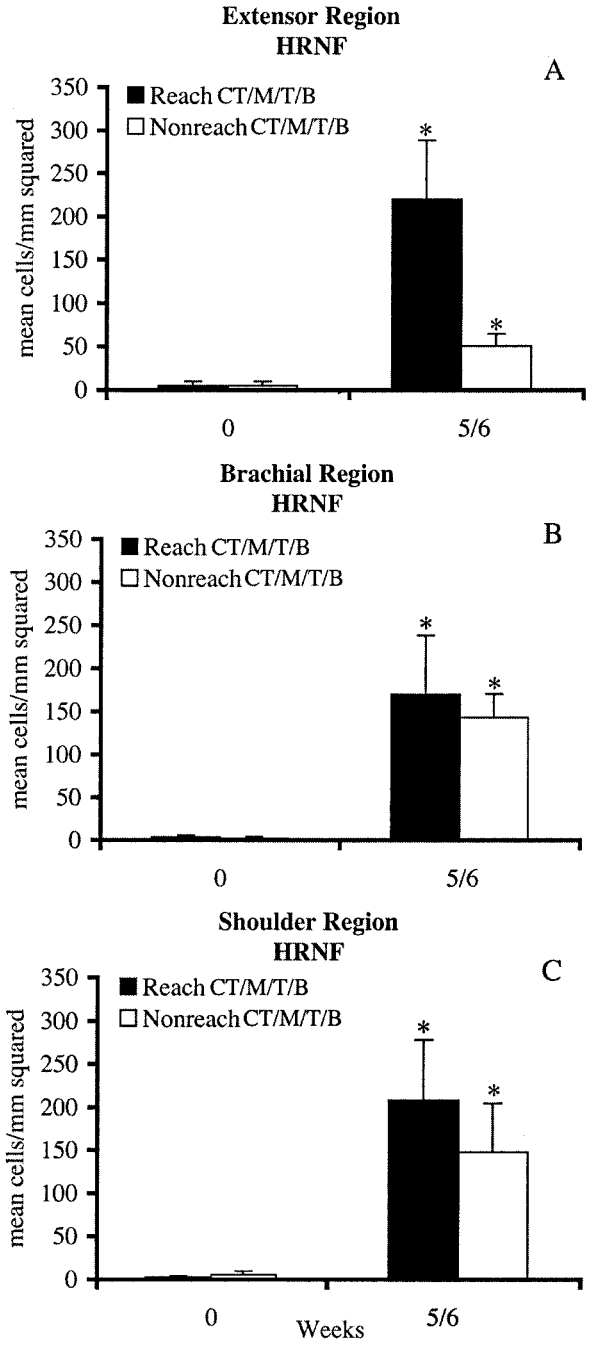

Figure 2. Average number of ED1+ (activated) macrophages + SEM, determined by bioquantitation, observed in tissues of proximal regions of the reach and nonreach forelimbs of rats that performed a high-repetition, negligible-force (HRNF) reaching and grasping task for up to 6 wk. The number of macrophages increased in these proximal tissues within the same time frame as increases in more distal forelimb tissues. A) Extensor muscles of the proximal forelimb. B) Distal humerus. C) Scapula. *$P < 0.05$ compared with 0 wk controls. CT, loose connective tissue; M, muscle; T, tendon. [Adapted from Barbe, M.F., A.E. Barr, I. Gorzelany, M. Amin, J.P. Gaughan, and F.F. Repetitive motion causes local injury, systemic inflammation and reach pattern decrements in rats. *J. Orthop. Res.* 21:167–176, 2003. Copyright © 2003 Orthopaedic Research Society. Used with permission.]

exposed equally on both sides due to a weight shift to execute the forelimb reaching movement; or 2) a systemic mechanism of injury was responsible for the tissue pathology in the relatively unexposed, nonreach forelimb. To test these hypotheses, tissues at other anatomical sites were examined for exudate macrophages and proinflammatory cytokines. Cytokines are chemical mediators that function in inflammation by attracting monocytes and macrophages to an injury site and by stimulating the proliferation of immune and other cell types. For example, the proinflammatory cytokine interleukin-1 (IL-1) is produced by monocytes and macrophages, as well as numerous other cell types (7). This cytokine is multifunctional and upregulates the production of many proteins, including matrix metalloproteinases that degrade extracellular matrix components (13). Cytokines are known to work through both autocrine and paracrine mechanisms, and they affect sites at some anatomical distance from an injury through circulatory distribution (7,15).

In addition to their increase in distal forelimb tissues, macrophages also became more numerous in proximal tissues of both the reach and nonreach forelimbs with chronic performance of a highly repetitive reaching task (1,3) (Fig. 2). In the case of the reach limb, this arguably could be the result of exposure of proximal tissues during task performance, which required maximum glenohumeral elevation and elbow extension. However, the weight shift observed toward the contralateral (nonreach) limb did not typically require an extreme forelimb motion, and it usually was accomplished by placing the open forepaw against the wall of the pen rather than by the acceptance of weight onto the forepaw against the floor of the pen. Therefore, the findings

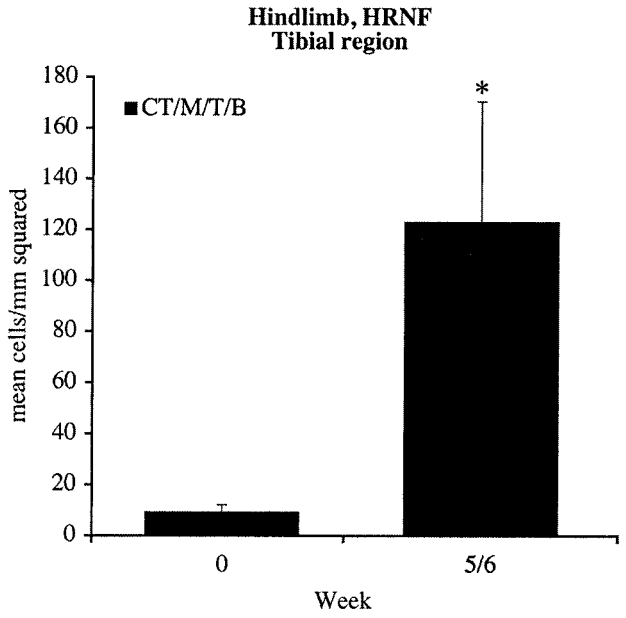

Figure 3. Average number of ED1+ macrophages + SEM, determined by bioquantitation, in the tissues of the tibial region of rats that performed a high-repetition, negligible-force (HRNF) reaching and grasping task for up to 6 wk. The number of macrophages increased in these hindlimb tissues within the same time frame as increases in the forelimbs. *$P < 0.05$ compared with 0 wk controls. CT, loose connective tissue; M, muscle; T, tendon; B, bone. [Adapted from Barbe, M.F., A.E. Barr, I. Gorzelany, M. Amin, J.P. Gaughan, and F.F. Repetitive motion causes local injury, systemic inflammation and reach pattern decrements in rats. *J. Orthop. Res.* 21:167–176, 2003. Copyright © 2003 Orthopaedic Research Society. Used with permission.]

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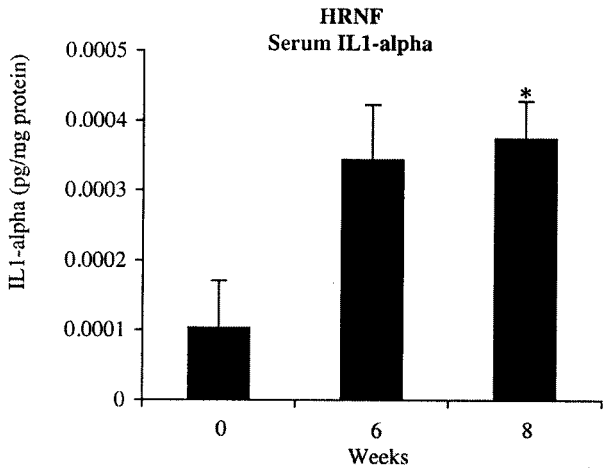

Figure 4. Average levels of IL-1α protein, expressed as a proportion of total protein, + SEM in the serum of rats that performed a high-repetition, negligible-force (HRNF) reaching and grasping task for 6–8 wk. *$P < 0.05$ compared with 0 wk controls. (Reprinted from Barbe, M.F., A.E. Barr, I. Gorzelany, M. Amin, J.P. Gaughan, and F.F. Repetitive motion causes local injury, systemic inflammation and reach pattern decrements in rats. *J. Orthop. Res.* 21:167–176, 2003. Copyright © 2003 Orthopaedic Research Society. Used with permission.)

of increased numbers of macrophages in brachial and scapular tissues seemed out of proportion to the exposure level for the contralateral, nonreach limb. Furthermore, examination of hindlimb tissues also showed significant increases in numbers of macrophages at 5 to 6 wk of task performance (1) (Fig. 3). Hindlimb involvement was even less intense than nonreach forelimb involvement in this task. Typically, rats sat in front of the food dispenser tube with their weight distributed among all limbs, waiting for a signal to attempt a reach. During the reach, the forelimbs were lifted, so a transient weight shift onto the hindlimbs occurred, and the nonreach limb was placed on the chamber wall while the reach limb was extended to the target. Since the target height was equal to shoulder height in the quadruped position, it was not necessary to extend the hindlimbs to accomplish the task. Therefore, the task required only a low level of hindlimb exertion performed at midrange of all hindlimb joints. The presence of inflammatory macrophages in these relatively uninvolved hindlimb tissues was surprising, and led us to explore further the possibility of a systemic effect.

The serum of rats was assayed for the proinflammatory cytokine interleukin-1 alpha (IL-1α), a subtype of IL-1. Serum IL-1α was significantly elevated at 8 wk after initiation of highly repetitive reaching (1) (Fig. 4). This finding convincingly revealed a systemic component to the inflammation, resulting from the performance of a highly repetitive, forelimb-intensive task. Regardless of whether the circulating cytokine was stimulated by exposure at multiple sites (*i.e.*, the bilateral forelimbs and hindlimbs), or simply by intense exposure at a primary site (*i.e.*, the reach forelimb), once it entered the blood stream it was distributed throughout the body with the potential for widespread effects.

The presence of inflammatory cells and mediators in many anatomical sites in our model may be evidence of such circulatory distribution and effect. In other words, although the task induced injury only in the reach limb, signs of inflammation are present in an anatomically widespread and bilateral pattern. This may be due in part to increased levels of IL-1α in the serum. The consequences of this widespread inflammation may have been signs and symptoms that were equally widespread and bilateral.

Studies examining the functions of IL-1 have reported a wide spectrum of biological properties, including induction of bone resorption, degradation of collagen in cartilage, recruitment of macrophages to injury sites through chemokine induction, and induction of inflammation- and sickness-hyperalgesia (7,8,13,15). These effects can be stimulated systemically through intravenous, intrathecal, or even intraperitoneal administration of IL-1 (15). Myeloid cells (circulating monocytes, tissue macrophages, and osteoclasts) are not only the primary sources of IL-1, but are also key cells recruited and/or activated by IL-1 (7). The increased numbers of macrophages in the hindlimb tissues of our rats in the presence of increased serum levels of IL-1α may be interpreted as evidence of a systemic proinflammatory cytokine effect induced by repetitive upper limb motion.

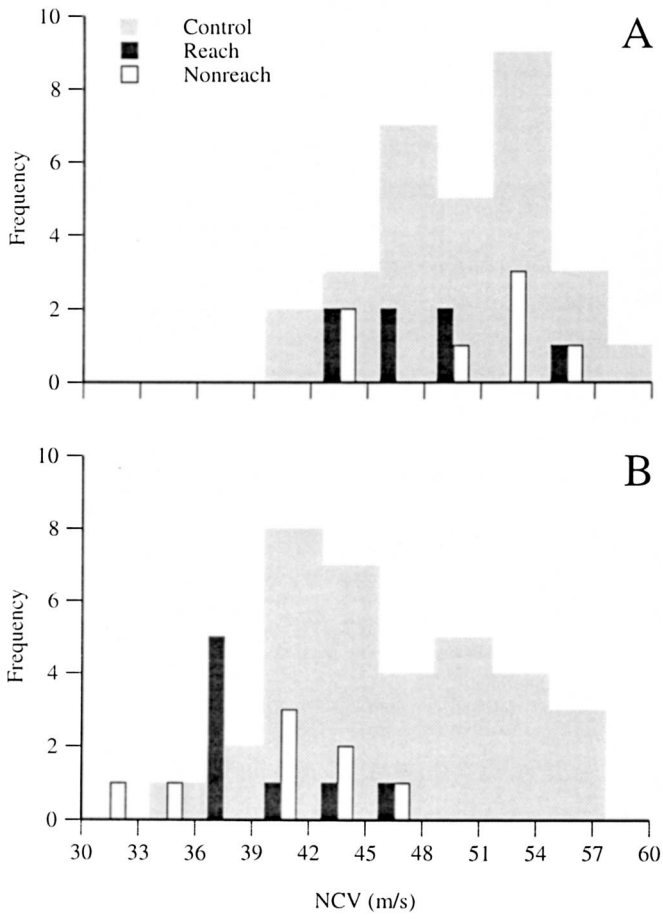

Figure 5. Nerve conduction velocity (NCV) measurements of the median nerves of the reach and nonreach forelimbs of rats that performed either A) a high-repetition, negligible-force (HRNF) or B) a high-repetition, high-force (HRHF) task for 9–12 wk compared to 0 wk controls. The mean median nerve NCV of the reach limb is significantly lower than controls for both the HRNF and HRHF exposures ($P < 0.05$). The mean median nerve NCV of the nonreach limb is significantly lower than controls only at the HRHF exposure ($P < 0.05$).

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IL-1α has many other systemic effects, including fever, anorexia, immunosuppression, and tissue/protein catabolism (7,13,15). IL-1α in the serum might contribute to a vague sense of malaise (15). In our rat model, subjects were observed to refuse task participation for the full 2-h time period during the peak inflammatory response in weeks 5–8 (1,5,6). This lack of participation most often took the form of the animal curling up and falling asleep for some portion of the task session. Such behavior might indicate either malaise or decreased appetite, despite the control of subject weight gain through food deprivation. Any clinician who has treated patients with WMSDs may be familiar with their descriptions of vague symptoms that shift from one anatomical region to another. While clinicians most often will dismiss such misbehaved symptoms and focus on the "exposed" anatomical region, such symptoms may well have a pathophysiological basis, namely the circulatory distribution of cytokines induced by a localized injury-inflammation cycle.

NEUROPHYSIOLOGICAL EFFECTS OF REPETITIVE MOTION

There is a dose-dependent response of the median nerve to a repetitive reaching task in rats (5,6). A significant reduction in the conduction velocity of the median nerve of the reach limb was detected after 12 wk of exposure to a highly repetitive task with or without high force (Fig. 5). The neurophysiological response was bilateral, with performance of a high-repetition, high-force (HRHF) task. The reduction in nerve conduction velocity (NCV) persisted beyond the 8-wk time point at which the inflammatory response had begun to resolve. In addition to the decline in NCV, a loss of forepaw skin sensitivity, determined using Von Frey filaments, was detected in both the reach and nonreach limbs of HRHF rats (Fig. 6). Again, the bilateral NCV and sensory changes could be attributed to bilateral exposure. However, also shown in Figure 6 is a loss of skin sensitivity of the hind paw with time, indicating a possible systemic reaction.

Since proinflammatory cytokines, such as IL-1α, are known to induce hypersensitivity rather than hyposensitivity (15), the sensory findings in our model are inconsistent with a direct cytokine-mediated effect. The decline in NCV of the median nerve could certainly explain the hyposensitivity of the forelimbs, but peripheral nerve compression of the five peripheral nerves that serve the plantar aspect of the hind paw (*i.e.*, the medial and lateral plantar nerves, the sural nerve, the tibial nerve, and the saphenous nerve) seems unlikely, particularly at the low exposure levels for the hindlimb. Again, the hindlimb sensory loss pointed toward a hypothesis for a systemic effect, albeit a different response than one induced by proinflammatory cytokines. One possible mechanism for such a systemic effect with regard to nerve compression is the upregulation of growth factors, such as connective tissue growth factor (CTGF), or transforming growth factor beta (TGF-β), which lead to the overproduction of collagen. Collagen synthesis in and around peripheral nerves can contribute to compression, which can adversely affect conduction velocity (9). Figure 7 shows that CTGF was upregulated in the median nerves of both reach and nonreach forelimbs with performance of a highly repetitive task, and that collagen type I synthesis concomitantly increased (5,6). This could be explained by a bilateral exposure effect. However, like IL-1α, CTGF is known to be distributed through the circulatory system and to induce generalized collagen production (12). Inflammatory cells, such as macrophages, also secrete CTGF (10). The discovery of increased levels of CTGF and collagen type I in the tissues of exposed rats leads us to ask whether the loss of sensation in the hind paw is caused by peripheral nerve compression due to collagen overproduction. This question has yet to be experimentally tested.

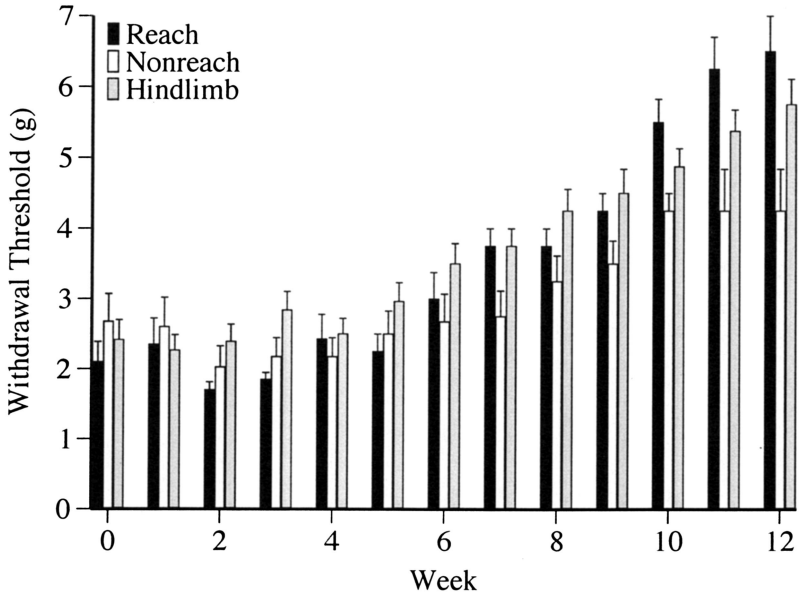

Figure 6. Threshold force + SEM for paw withdrawal, tested using Von Frey monofilaments, for rats that performed a high-repetition, negligible-force (HRNF) reaching and grasping task for up to 12 wk. Sensory threshold increased significantly in reach and nonreach forepaws as well as in hind paws at week 12 compared to weeks 0 and 6 ($P < 0.05$).

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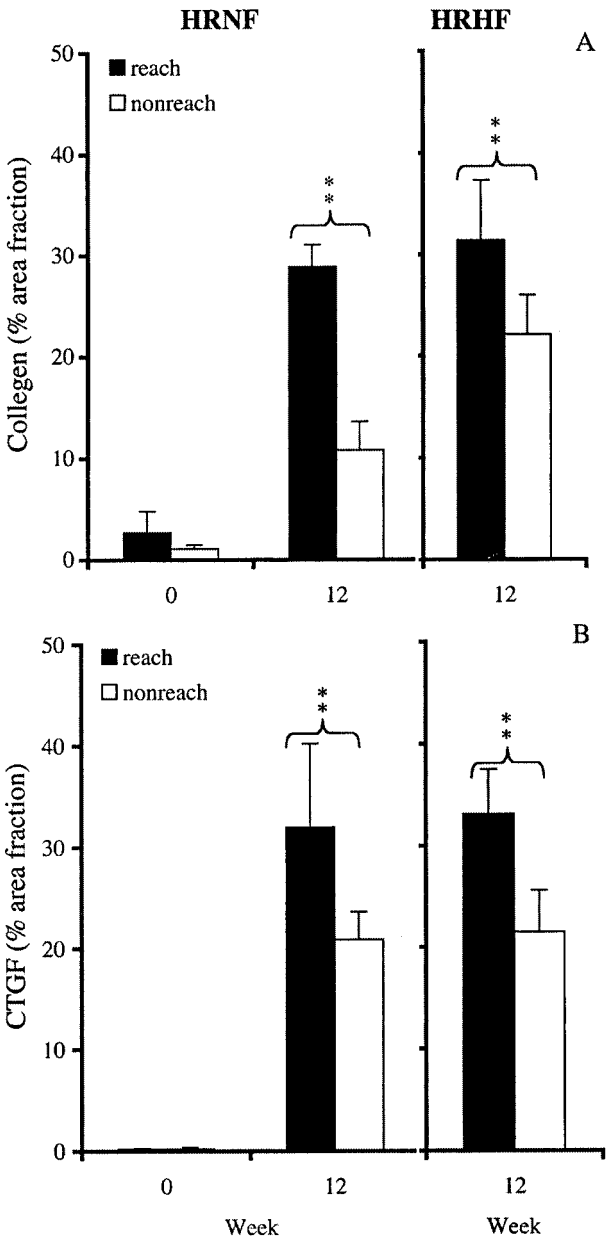

Figure 7. Quantification of area fraction containing A) collagen type I and B) connective tissue growth factor (CTGF) immunoreactivity in the median nerve at the level of the carpal tunnel in the reach and nonreach forelimbs of rats that performed either a high repetition, negligible force (HRNF) or a high-repetition, high-force (HRHF) task for 12 wk compared to 0 wk controls. $^{**}P < 0.05$.

LOCALIZED INJURY INDUCES A SYSTEMIC INFLAMMATORY RESPONSE

While it is impossible to rule out the potential for simultaneous local and systemic inflammatory responses in our rat model, there is no doubt that a systemic response is present. The elevation of serum IL-1α proves this assertion (1). Undoubtedly, the response of tissues to highly repetitive and/or forceful tasks is complex, involving multiple mediators (cytokines and growth factors) in addition to those we have studied. However, the inflammatory and fibrogenic indicators we have followed suggest a mechanism whereby localized exposure to a highly repetitive forelimb-intensive task induces a local injury followed by an inflammatory response, which in turn induces systemic inflammatory, fibrotic, and osteolytic responses that increase the susceptibility of tissues at anatomical sites distant from the original injury site. In other words, the presence of circulating proinflammatory cytokines increases the gain of the inflammation cycle so that previously innocuous stimuli initiate an inflammatory response at other anatomical sites, and the presence of circulating fibrogenic and proinflammatory mediators, such as CTGF and IL-1, causes collagen production that encroaches upon healthy tissues. This proposed mechanism is depicted in Figure 8. The cycle of chronic systemic inflammation and fibrosis instigated by a repetitive task-induced injury is responsible for widespread symptoms that are difficult to classify on physical examination. The symptoms may also be transient in nature for several reasons that are indicated in Figure 8. Proinflammatory mediators stimulate the production of antiinflammatory cytokines, such as IL-10, which in turn downregulate the proinflammatory cytokines. This cascade of events brings about the natural resolution of an inflammatory episode. In the absence of a persistent injury stimulus, the inflammation may be completely resolved, with the affected tissues restored to their preinjury state. In our rats, the reduced participation in the task during the peak inflammatory phase may have helped quell the inflammation and promote such tissue recovery. In the case of severe injury or persistent injury stimulus, a chronic inflammatory phase will ensue. Injured tissue may be replaced with a fibrotic scar, resulting in loss of function in that tissue or compression of surrounding tissues, such as peripheral nerves. In both our own and another animal model of chronic exposure to highly repetitive motion, fibrosis in the form of increased collagen deposition or collagen cross-linking occurs in various musculoskeletal and neural tissues regardless of resolution of the acute inflammatory episode (2,5,6,14).

CLINICAL IMPLICATIONS IN THE MANAGEMENT OF WMSDS

There are numerous clinical implications of our hypothesis that systemic inflammation and its sequelae are at the root of widespread and puzzling symptoms in patients with WMSDs. Clinicians should not dismiss such complaints by patients, because they have a pathophysiological basis. Denial of a patient's complaints strains the therapeutic relationship and frustrates successful intervention. Such widespread symptoms may indicate increased susceptibility of uninjured tissues; they should be a focus of preventive treatment that might include the simultaneous reduction of injury stimuli (*i.e.*, of repetitiveness and forcefulness) and attenuation of systemic inflammation. The combination of these interventions is likely to be more effective than treatment of systemic inflammation alone, since inflammation is a normal response to tissue injury. Unfortunately it is far more common for workers to take nonsteroidal anti-inflammatory medications and keep working than to take such medications and rest. Clinicians should educate their patients about the potentially detrimental long-term effects of taking antiinflammatory

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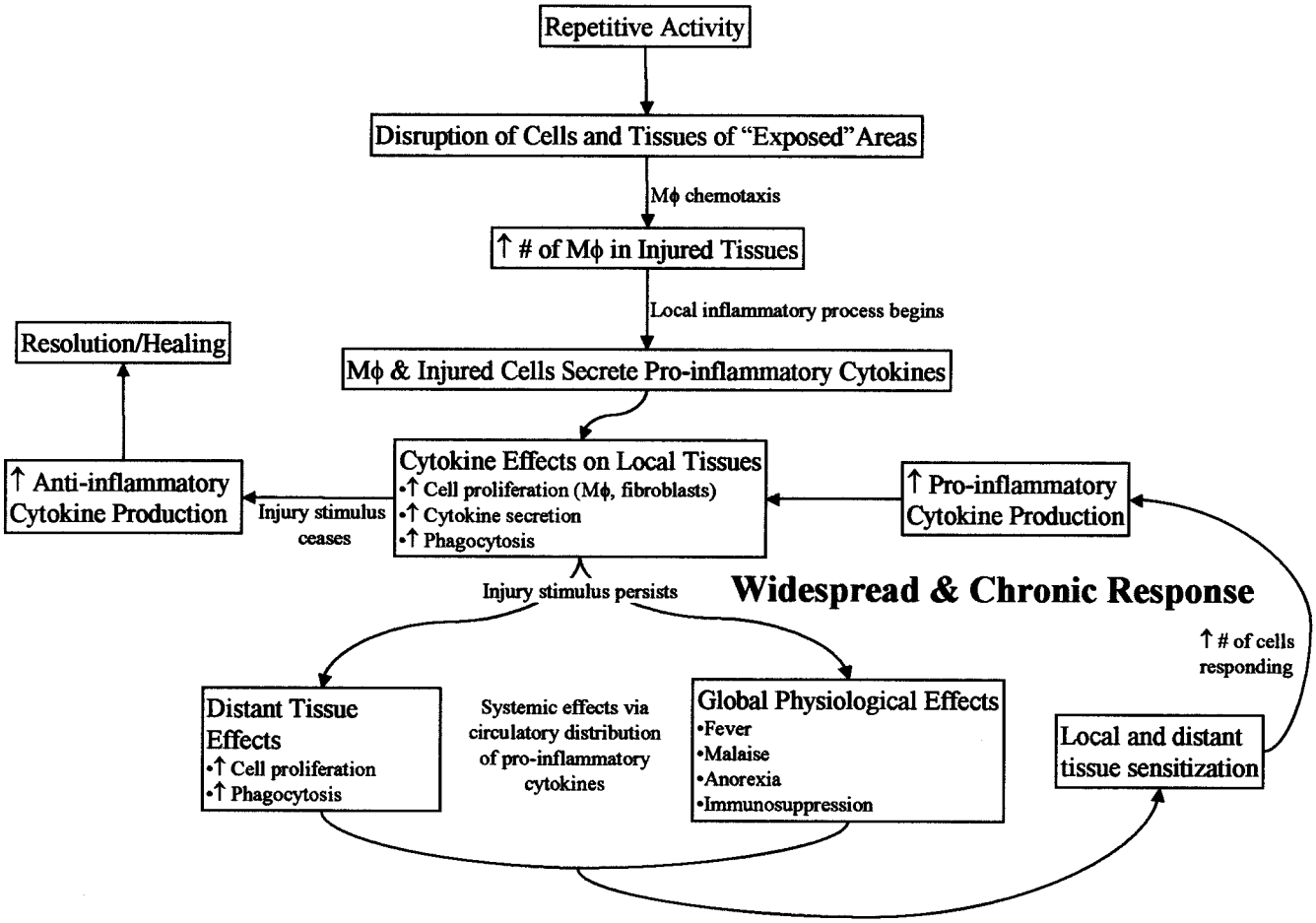

Figure 8. Proposed mechanism for the role of systemic distribution of cytokines in widespread WMSD symptoms. A unilateral, repetitive activity induces a localized inflammatory response. If the injury stimulus ceases, an acute inflammatory episode is resolved, and healing occurs. If the injury stimulus persists, circulating cytokines will have effects on tissues not directly involved in task performance, or will have global physiological effects. Initiation of the systemic response sensitizes tissues, both local and distant to the injury stimulus, and causes further upregulation of proinflammatory cytokines. Hence the cycle of widespread and chronic effects is propagated. ↑ , increase; Mϕ, macrophage.

medications while continuing to perform high-risk occupational tasks. Since our studies in the rat have explored the early onset and development of WMSDs due to repetitive motion, the findings also support the use of a training period for employees who will be performing a new high-risk work task. Although we have yet to determine the long-term effects of performing a highly repetitive task, we and others have been able to induce chronic inflammation and fibrotic scar formation in as little as 6–12 wk (2,5,6,14). Such tissue changes should be avoided, as scarring may permanently disrupt normal musculoskeletal and neurological function.

SUMMARY

Several important conclusions can be drawn from our rat model of hand-intensive repetitive motion. Tissue injury is dose dependent and is induced by highly repetitive reaching and grasping tasks with low or high force. A localized inflammatory response occurs in exposed tissues, and behavioral indicators of discomfort coincide with this inflammatory response. The inflammatory response affects tissues in a widespread bilateral pattern that is instigated by a combination of local and systemic cytokine and cellular effects. Despite resolution of the early inflammatory response, CTGF and IL-1α are persistently upregulated, as is the production of collagen. The production of collagen contributes to loss of peripheral nerve function by compressing neural tissues. This fibrotic reaction seems to occur in the same bilateral and widespread pattern seen in the inflammatory response. Such widespread reactions to a unilateral, hand-intensive task may cause confusing signs and symptoms that defy diagnostic criteria for WMSDs, and might lead to inadequate clinical management. Practitioners should consider the possibility of widespread effects when examining and treating patients with WMSDs associated with unilateral tasks (11).

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