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Original Articles
Review & Analysis: Musculoskeletal

Musculoskeletal Rehabilitation: Current Understandings and Future Directions.
Timothy R. Dillingham, MD, MS

Physiological Basis of Fatigue.
William J. Evans, PhD; Charles P. Lambert, PhD

Muscle Pain Syndromes.
R Norman Harden, MD

Low-Back and Neck Pain Diagnosis and Treatment.
Rowland G. Hazard, MD

Musculoskeletal Problems as Comorbidities.
Hilary C. Siebens, MD
Musculoskeletal Research Conference Summary Report


Key Words: Musculoskeletal, Research, Disabilities, Rehabilitation Issues

INTRODUCTION AND OPENING REMARKS

A 2-day conference on “Musculoskeletal Research” brought together 55 national experts in the field, including clinicians, academicians, and researchers, to establish recommendations for a federal research agenda on nonoperative and postoperative musculoskeletal interventions. The meeting, which took place at the Bethesda Hyatt Regency Hotel on January 9–10, 2006, was jointly sponsored by the National Center for Medical Rehabilitation Research (NCMRR), the National Institute on Aging (NIA), the National Institute on Arthritis and Musculoskeletal Diseases (NIAMS), the Social Security Administration (SSA), and the Interagency Committee on Disability Research (ICDR). This event provided a forum for an interesting exchange of ideas and establishment of research priorities on a topic that has received relatively little attention in the past.

Planning began 18 mos ago when NCMRR Director Michael Weinrich met with colleagues from the American Academy of Physical Medicine and Rehabilitation (AAPM&R). Because the majority of Americans with disabilities suffer from musculoskeletal problems and because a rapid expansion of clinical procedures continues despite a limited evidence base, AAPM&R representatives and Weinrich agreed there was a need for a federal musculoskeletal research agenda. The ICDR took an interest when language inserted in a Senate report asked them to pay special attention to musculoskeletal research across federal agencies, identifying research gaps. With these joint goals in mind, Weinrich hoped research priorities from this meeting would establish a strategic plan for NCMRR to lend focus to the field and influence other institutes and agencies, shaping their priorities as well.

Conference participants received working papers (included with this report) before the meeting to support the discussion in each of the relevant breakout groups. The topics included:

- Musculoskeletal Rehabilitation: Current Understandings and Future Directions
  Timothy R. Dillingham;
- Physiologic Basis of Fatigue
  William J. Evans and Charles P. Lambert;
Jay Magaziner, University of Maryland

Jay Magaziner outlined the epidemiologic approach to musculoskeletal research, identifying a framework for issues related to prevention of disability. He focused on disablement and the recovery process in examining models for targeting preventive strategies. Prevalence, risk factors, and consequences of the three major areas of musculoskeletal concerns were discussed, including two conditions with gradual decline, i.e., osteoarthritis (OA) and back pain, and one condition with sudden decline and expectations for recovery, i.e., osteoporotic hip fracture.

Magaziner defined epidemiology as the study of the distribution, causes, and consequences of disease and disability and the evaluation of preventive interventions in populations. Expanding the distributions of disease to include disability, he added that epidemiologists identify causes and risks for disease and disability and evaluate strategies for prevention. A public health prevention model identifies and evaluates interventions to prevent occurrence, progression, and adverse consequences of diseases and disabilities in the population. Disability prevention is an aspect of the tertiary progression of this model, defined as interventions directed at reducing adverse consequences and maximizing function in those with clinically apparent disease. Less effort is directed in this area (as is reflected in the NIH budget), requiring a framework with a broader perspective.

Leading causes of disability in the United States are arthritis and rheumatism and back or spine problems, which represent more than 30% of disablement. Musculoskeletal problems are second only to heart disease in costs expended for chronic conditions. The indirect costs of musculoskeletal conditions are greatest in middle age, as calculated in lost wages when a person is unable to work; later, direct costs are reflected in long-term care. Data from the National Center for Health Statistics using statistics from the United States Census indicate that 45 million people suffer from arthritis, whereas 75 million people suffer low back pain.

In 2001, nearly 70 million adults reported having OA or chronic joint problems. Risk factors include heredity, age, weight, gender, and trauma. Consequences include pain in the knee and hip and swollen joints, limited motion, and difficulty with activities of daily living (ADLs). Although there is no cure, the goal is prevention and minimizing adverse effects. Magaziner noted the evidence-base for intervention is too broad-based to explore in the context of this conference.

Low back pain strikes 84% of the United States population and is the most frequent musculoskeletal problem in people 75 yr and older. Risk factors include lack of exercise, excessive weight, smoking, occupational factors, back and abdominal muscle weakness, and spinal stenosis. It often results in depression, reduced activity, and poor quality of life. Treatment methodologies include behavior...
modification, manipulation, and medication. Slowing progression toward functional limitations helps prevent disablement.

Osteoporosis strikes three times as many women as men older than the age of 50, with a much greater percentage of women exhibiting reduction in bone mass. When complicated by hip fracture, functional consequences include loss of neuromuscular function, difficulty with instrumental tasks, increases in cognitive deficits and depressive symptoms, and changes in social function. A focus on fracture prevention creates a gap in better understanding treatment strategies.

Future directions must focus on identifying specific deficits as well as optimally timed targeted interventions; developing a better understanding of the mechanisms underlying deficits and mechanisms by which interventions operate; and developing evidence for efficacy and effectiveness of interventions in populations.

Discussion

A contentious issue in aging research is the inherent value of weight loss. Studies indicate that although it may increase mortality and hip fractures, it may be a recommended intervention for OA and low back pain. Magaziner doesn’t believe that weight changes significantly during recovery from hip fracture; instead, there is muscle loss and increased fat. No known evidence was cited that lean people recuperate faster.

Magaziner did cite work with home-exercise interventions that did not change muscles and bones as hoped; instead, the protocol facilitates a mastery of exercise, boosting feelings of self-efficacy and a confidence level conducive to greater activity and participation levels. Possible biological or chemical changes also may influence cognitive abilities.

In reference to the epidemiology of OA, there was concern expressed as to how that diagnosis is made and whether there is a confounder based on self-report. Magaziner is in agreement that the available data present significant limitations.

Magaziner clarified that the goal of recovery is to get a person up and functioning. In the stroke population, for instance, there may be a need for both aerobic capacity and strength training. Both will bring about a change in walking ability. The process of recovering from hip fracture is similar because both gait and strength need to be in good order. The question is how to design a program that people will incorporate in their everyday lives.

To better understand the relationship between impairment and functional limitations, one must conceptualize movements as a complex integration of strength and neurological integrity that produces actions incorporated into ADLs. The American Physical Therapy Association published a validated instrument in June 2005 looking at movement that underlies ADLs. That instrument has two dimensions: difficulty and self-confidence. It is the integration of musculoskeletal structural integrity and attitude that create confident movement and independent ADLs. Movement might therefore be a better focus for discussion. Magaziner agreed, adding that if movement is a central theme, the next step is to promote advance in movement abilities to help people progress.

A patient’s performance is measured through completing tasks and not through measuring impairment or function, which are abstract notions that don’t apply to the complexities in patients. Weinrich believes researchers should be honest about the limitations and state that they are measuring task performance only.

Behavior Change

Susan Bartlett, Johns Hopkins University

Susan Bartlett emphasized the need to integrate behavioral science into medical interventions that work well in small clinical trials but fail when moved to the community. Adherence to prescribed interventions is relatively poor, even when people understand the importance of watching diet and controlling alcohol intake. Bartlett used arthritis and weight as a model for behavior change because data show that for every 2-pound increase in weight, the risk of developing arthritis is increased by 9–13%. Among adults, the prevalence of significant knee, hip, and back pain increases markedly with body mass index.

More than 50% of Americans are now overweight and in some states a quarter of the population is obese. A meta-analysis conducted at Hopkins showed that weight loss is an uncommon occurrence, with only a small percentage of people able to lose 10% of their body weight and keep it off for a year. Exercise is the best predictor of who will stay lean, but exercise alone doesn’t work. Only 15% of the population exercise at a level to derive health and physical fitness, and a quarter of the population is completely sedentary.

Realizing the value of weight loss, after it was shown to improve function and decrease pain in people with OA by investigators at Wake Forest University, Bartlett looked at the usefulness of lifestyle physical activity instead of structured exercise. She surmised that building increased activity into a routine day is a better way to create a more sustainable exercise routine. It encourages people to move by creating the opportunity for intermittent periods of physical activity and can prompt people to expend the same energy as they might during a dedicated period of time.

In an early study of obese people, Bartlett compared the efficacy of lifestyle physical activity
against aerobic activity. The results showed that people who incorporated lifestyle physical activity into their lives lost comparable weight to those who did aerobic activity three times per week. There was also a trend in the lifestyle group to continue this pattern of physical activity. Bartlett applied these lifestyle changes to the model of arthritis, hypothesizing that by using a comprehensive weight-loss program in combination with lifestyle activity in people with verifiable knee OA, individuals would see significant improvement in symptoms and functioning.

In the intervention group, Bartlett and colleagues found that individuals lost an average of 15 pounds, whereas the control group remained weight stable. There was a decrease in pain (40%) and stiffness (46%) and increase in function (50%). In women, there were robust findings with even small amounts of weight loss. Effects exceeded those achieved with analgesics, without side effects. They concluded that even small amounts of weight loss for persons with mild-to-moderate knee OA can make a profound difference.

This challenges goals physicians have previously set for obese patients in treatment. NIH clinical guidelines now suggest an initial weight loss of 10%, then a focus on maintenance, signifying that small amounts of weight loss can make a difference. The definition of exercise also can be broadened; it does not have to be continuous to be beneficial. In addition, creative exercise scenarios can be effective.

Discussion

Bartlett was asked, if the goal is weight loss through exercise, are the changes in symptoms caused by the positive effects of exercise or weight loss and whether it is possible to do a study in which people exercise but also increase their intake and maintain weight to see whether symptoms still decrease. She indicated they have examined these variables that in other studies, although not in patients with arthritis. If exercise is increased without tight control of portions, weight doesn’t change. Exercise is connected with a modest decrease in pain and improvement in functioning, but only 5–8%. It is the weight loss that is primarily responsible. Only two studies in North America have looked at this in an empirical way. There is still more work to be performed in this area.

If people don’t maintain the weight loss, are they any worse off than they were before, or is it the gaining of weight that is problematic? Bartlett is following patients 1 yr later but was unable to discuss that data. Physiologically and metabolically, it is problematic to lose weight and to regain it. They have a proposal under review to use magnetic resonance imaging to look at rate of cartilage turnover as people are losing weight to determine whether they are changing structure. They are not sure of the mechanism.

Epidemiologic studies have shown that there is no increased risk of heart disease and diabetes among obese people if they are physically active. Because weight loss is so difficult, increasing physical activity is far more effective in decreasing risk and increasing function than losing weight. Bartlett agreed that there is no evidence that if you lose weight, you decrease your risk. Simply increasing physical activity without weight loss also may be beneficial. In patients with knee OA, reducing the load through the knees makes the difference. Early results indicate that symptom reduction is related to a change in weight.

In response to a question about why with so little relative weight loss there is so much benefit, Bartlett responded that for women identity is connected to weight in ways that don’t occur with men. When they feel in control and are turning things around, there are positive psychological benefits. As women feel better, they move more.

Evidence shows, according to Bartlett, that as you exercise more, you eat less. Athletes, for instance, maintain a stable body weight. It is environmental factors that push people toward being overweight and obese and a lack of physical activity is associated with appetite deregulation.

Promising Scientific Areas and Emerging Technologies

Mary Ann Keenan, University of Pennsylvania

Keenan focused on the biology of musculoskeletal problems, stating it is critically important to accelerate fracture healing to minimize pain and time of inactivity. Her PowerPoint presentation included promising scientific methods. For instance, autologous blood concentrates have been approved for marketing by the Food and Drug Administration, but there is little clinical evidence to support their use. More positively, vascular endothelial growth factor has been found to improve healing in a mouse femoral fracture model and a rabbit radial defect model.

Bone morphogenetic proteins (BMPs) are the most powerful osteoinductive factors known at this time. BMP-7 (osteogenic protein-1) has been approved for the treatment of long-bone nonunions, and BMP-2 has been approved for spinal fusion. A limitation is requiring implantation in the fracture site via an open surgical procedure. A less-invasive procedure consists of injecting BMP-2 into closed femoral fracture sites in rats; it has shown significant acceleration of fracture-healing by biomechanical and histologic criteria.
Promising new methods are positively affecting bone healing. Demineralized bone matrices retaining collagen and growth factors are used to improve spine fusion, treat fracture nonunions, and fill osteolytic lesions around total joint implants. TP508 (Chrysalin), a new synthetic peptide, enhances bone formation in preclinical models. Although there has been focus on the bone, a fracture causes significant muscle injury as well. New techniques for healing muscle include suramin, an antiparasitic and antitumor drug that inhibits fibrous tissue formation and improves muscle healing after injury. Another compound, relaxin, promotes improved muscle healing with a greater number of regenerating myofibers in a mouse muscle-strain injury model.

Most clinical scenarios require the treatment of muscle fibrosis after it has already developed, prohibiting efforts at prevention. Work is now being done to inject matrix metalloproteinase-1 (MMP-1, collagenase) into an area of fibrosis after muscle injury, and the findings suggest the potential to treat muscle injury after scar tissue has formed. Clinical applications include rotator cuff tears.

Tissue engineering is another area in which important work is occurring. Variables considered during the preimplantation incubation period include the following:

1. Type of cell used;
2. Material into which the cells are seeded;
3. Factors to which they are exposed; and
4. Loading conditions to which they are subjected.

Studies have been done on bilayered tissues and mesenchymal stem cells, with the latter suggesting that a single population of mesenchymal stem cells can lead to in vivo production of a cartilage/bone composite. Bioresponsive materials respond and remodel upon receiving biological signals from newly forming tissue. Their advantage for use as scaffolds is that they allow for the generation of new tissue in tandem with scaffold resorption. Current limitations of this preliminary work in musculoskeletal research are listed in the PowerPoint presentation, as are bone substitutes.

The new imaging techniques, Fourier transform infrared spectroscopy and $^{31}$P solid-state nuclear magnetic resonance imaging, will help to promote a better understanding of osteoporosis. Combining these tools will lead to a more complete indicator of the risk of bone fracture than is provided by bone mineral density measurements. Future work includes a biology-based approach to improve structure and accelerate healing to improve function. Other areas requiring research are orthotic technology for lightening devices and nerve transfers.

Discussion

In responding to a question on the relationship between fracture healing and clinical and socioeconomic outcomes, Keenan responded that if fracture healing is accelerated, then all other recoveries are hastened as well, leading to a decrease in disability and muscle weakness and improvement in muscle flexibility, ligament and joint functioning and pain control. With hip fractures, patient pain has limited the clinician's therapeutic ability. These new techniques will positively impact socioeconomic factors.

In reference to tissue-engineered constructs, clinicians will have to determine how to rehabilitate patients who eventually receive them. Keenan was asked whether, in the animal models, there is any control over weight-bearing activities the subject engaged in or whether it is a factor. She responded that they cannot control for animal activity and that it is not practical to be in a non-weight-bearing state. To rehabilitate, one must be mobile and engaging in weight-bearing activity. Stability can be achieved through bone substances and gradually transitioning to true biological tissue.

PROMISING SCIENTIFIC AREAS AND EMERGING TECHNOLOGIES

The Trans-Rehabilitation Research Domain Research Model

Steven Stanhope, The National Institutes of Health

Overview

Dr. Stanhope opened his remarks by stressing the need to approach medical rehabilitation musculoskeletal research from a disablement/enablement process perspective. He then used a series of conceptual rehabilitation research models to underscore the opportunities and research gaps in this field. Dr. Stanhope used a mature biomedical research program model to indicate the diversity and divergent nature of technical and clinical activities and the increased challenges when such models are applied to a disablement/enablement musculoskeletal research model. Dr. Stanhope concluded with an example of an NIH movement sciences-based transdomain research program, which has effectively filled research gaps by merging science in the impairment, functional limitation, and disability rehabilitation research domains.

Presentation

A research priority model that was created by the scientific director for the Intramural Research Program at NIH was used to outline the typical components of a mature biomedical research program. The pyramidal shape depicts clinical research sitting atop three supporting levels: the
development and applications of advanced technologies, new directions in basic laboratory research, and translational research. From a bioengineering perspective, this model is driven from the bottom up in support of clinical research. Clinical scientists, on the other hand, drive this model from the top down with the hope of answering important clinical questions. The ideal biomedical research setting is one in which a multidisciplinary cohort of scientific staff, having sufficient knowledge, skills, abilities, and resources to support each level of the model, actively collaborate (Fig. 1).

Dr. Stanhope went on to indicate the primary gaps in musculoskeletal rehabilitation research emanate from the desire to understand the cause-and-effect relationship among the rehabilitation research domains. Simply stated, the disablment process, i.e., pathophysiology causes impairments, results in functional limitations and ultimately physical disabilities. Positively impacting musculoskeletal function at the pathophysiology and/or impairment levels with the hope of reversing the disablment process is one method for rehabilitation services to evoke the enabling process. Dr. Stanhope went on to effectively merge the biomedical research model with the rehabilitation research model to illustrate the multidisciplinary complexity and technical challenges when the goal is to investigate these trans-domain relationships and processes (Fig. 2).

The Physical Disabilities Branch is committed to implementing a trans-rehabilitation research domain model focused on the impairment, functional limitation, and disability rehabilitation research domains. Dr. Stanhope outlined a method in which the key is to obtain measures in the functional limitation domain that directly link to measurements, interventions, and outcomes in the impairment and disability domains. In essence, the concept in the transdomain model approach is in trying to connect the (rehabilitation domain) dots. He went on to demonstrate the central role clinical movement analysis (CMA) plays in determining these relationships. Modern CMA consists of three-dimensional motion capture, biomechanical modeling and analysis, and advanced compute simulation methods. In summary, CMA is capable of quantifying functional limitations, muscle-related movement control strategies, and relating these data to impaired strength levels and the strength and movement control patterns necessary to execute ALDs.

Reviewing a novel ankle-foot orthosis project, Dr. Stanhope gave an example using CMA to measure the extent to which the brace substitutes for or enhances weakened ankle muscles (impairment domain) and how the optimal brace design (relative to a patient’s physical characteristics and musculoskeletal impairment profile) can improve limb control (functional limitation domain), walking velocity and duration, and increase activity participation (disability domain). Dr. Stanhope concluded by demonstrating a novel method of customizing an ankle-foot orthosis to a patient’s individual characteristics and desired activity level is feasible and only realized when approached via realization of the trans-rehabilitation research domain model.

Discussion

Societal limitations involve cultural perspectives, where there is emphasis on external factors, such as drugs for healing. Although not discussed by Stanhope’s group, it is represented in a diagrammatic approach. Stanhope referred to research models and expressed how rehabilitation research must be interdisciplinary and connect with experts in other domains to understand the causes and effects in those domains. By quantifying the change in impairment, it may be possible to measure change in the functional limitation and, hopefully, the disability. Without the necessary tools, it is not always possible to measure the
impact of an intervention on an impairment. Although a patient’s response to treatment may be decreased pain and improved gait performance, the improved function may be caused by a compensatory strategy and not by enhanced function of the treated muscle or joint. CMA helps to identify the factors necessary for a person to perform an activity. However, the tools are lacking in the impairment domain that would indicate how the person could function at maximum capacity.

Stanhope added that curing disease in medicine requires great efforts at each level of the biomedical research model. From a rehabilitation research perspective, the complexity is much greater because like efforts must be undertaken in each of the rehabilitation research domains. However, comparatively few resources are in place to create musculoskeletal research infrastructure relevant to the trans-rehabilitation research domain model.

A comment referred to physical disability research as person-centered when moving from pathology and impairment into function; when moving on to disability it becomes a social construct. Rehabilitation is always engaged in issues of social justice, which are underfunded, relative to technologies. There is a constant cultural dialogue and even a cultural war because of its socially-constructed nature.

As short-term diseases become chronic diseases, according to another participant, the number one complaint is overwhelming fatigue. The National Cancer Institute, however, does not have one study section that looks at fatigue. This conference may want to set a broader research agenda as the treatment of the disease as pathophysiology is better understood. The disease may be cured, but the symptoms still remain.

Stanhope was thanked for the model presented and for deconstructing recovery. Disability is typically viewed as what one cannot do. By targeting basic research opportunities on a molecular level, we may better understand why some individuals recover with or without fatigue. This understanding may be extended from the molecular to the pathophysiologic to the societal level. This view of disability will help us deconstruct and analyze the process of recovery.

**NATIONAL INSTITUTES OF HEALTH**

**TRIAL DESIGN**

**Recurring Issues in the Design, Conduct and Analysis of Clinical Trials**

Susan Ellenberg, University of Pennsylvania School of Medicine

Ellenberg defined a clinical trial as an experiment that evaluates the effect of a medical intervention on a human being. Characteristics of clinical trials, including phases (i.e., 1–4), control groups, (placebo, active), treatment allocation (randomized, not), and treatment type (drug, device, vaccine, surgery, diet, exercise regimen), influence the design. She focused her discussion on the two biggest issues in interpreting results—bias and multiplicity. Bias refers to any tendency of the trial to generate findings that could be due to something other than the effect of the treatment. The goal is to minimize the bias that may arise from aspects of trial design, conduct, and/or analysis of results. Multiplicity arises when the researcher is looking at the data in many ways such that the chance of a positive result is increased even when there is no treatment effect.

Biassing a trial can occur many different ways. One example is placing patients with a better prognosis in the treatment group than in the control group. Trials with an objectively measurable outcome are less prone to bias, whereas trials in which physician or subject judgment is the primary outcome are more vulnerable. When designing trials, bias is controlled through randomizing to eliminate systematic differences between treatment groups. In conduct, it is optimal to “blind” or “mask” treatments to avoid bias in patient or physician assessment. In analysis, all enrolled subjects should be included and the analytical approach specified before collecting and observing data.

It is important to note that people with a disease or condition often get better on their own. When evaluating treatment effects, it is critical to be able to ascribe an effect to the treatment. Patients can report improvement as the result of a natural waxing and waning of symptoms over the course of time, placebo effects, a desire to please the physician, changes in adjunctive care, variability of response measures, “or regression to the mean.” Control groups are used to be sure that changes in status are actually caused by the treatment administered.

The “gold standard” in study design is placebo/sham controls, which most commonly are used in studies of new products when regulatory approval is sought. Active control trials compare one treatment (usually a new treatment) to another known to be effective. Historical controls are drawn from previous patient cohorts whose results are compared with results of a new treatment administered to a current cohort. Historical controls are used primarily when studying treatments for rare diseases, when there may not be adequate numbers to do a randomized trial. The use of historical controls requires meticulous accounting for the systematic differences between the current and past patient cohorts.

Concurrent but nonrandomized controls could include subjects who refuse the experimental treatment or select a different treatment and subjects treated by other physicians at the same or collaborat-
ing institutions. Selecting controls in this way creates a substantial risk that groups won’t have a comparable prognosis. In controlled trials, it is optimal to allocate treatments randomly to ensure that treatment groups have a similar prognosis and results won’t be biased in favor of one of the treatments.

It is ethical to randomize to a placebo when a subject is not at risk for an irreversible outcome if left untreated and/or when there is uncertainty about the treatment benefit. Placebos or shams are used because, in unblinded trials, the assessment of safety and efficacy could be affected by knowledge of treatment received. When it is impossible to blind the treatment, the effect of knowledge of treatment on trial results can be minimized by using objective outcome measures and having personnel who do not know the assigned treatment evaluate patients. All randomized subjects must be included in the analysis. To exclude subjects on the basis of what happened after randomization can severely bias results.

Multiplicity may occur when data are looked at in enough ways to find an occasional “statistically significant” difference: a false positive. It is therefore necessary when designing a clinical trial to prespecify the objective. Even when specifying an outcome, it is necessary to indicate statistically how the outcome will be tested. Multiplicity can be avoided by prespecifying principal study analyses; identifying primary, secondary and exploratory hypotheses; and prespecifying criteria for terminating study and performing final analyses.

Trials can be designed to improve efficiency, reducing time and cost without endangering validity. In a two-stage design, unpromising results in the first stage may be a reason for early study termination. When using multiple dose levels in the first stage, the most favorable dose can be selected for continuation. Futility designs include planned interim analyses at regular points in the trial with the strategy of abandoning the study if the probability of a positive outcome seems sufficiently low. Other ways to enhance efficiency include limiting data collection; developing programs to enhance compliance and reduce dropout; training research coordinators well; and use of appropriate software.

Adaptive designs allow changes to the protocol of an ongoing trial in response to the accumulating data. One type of “adaptation” involves modifying the design of the trial and the treatment allocation algorithm. An approach attracting interest allows the sample size to be enlarged if the emerging effect seems smaller than anticipated. A cautionary note is that adaptive designs require evaluation of accumulating data to see whether “adaptation” is warranted. Although review of some types of accumulating data does not cause problems, the review of interim efficacy comparisons present a threat to trial integrity if the results of these comparisons become known to investigators and others involved in the trial.

Clinical trials are resource intensive and can put subjects at risk. It is important to conduct trials that will maximize the opportunity for useful and credible results. Avoiding bias and multiplicity is essential if results are to be both valid and credible.

Discussion

When subjects are receiving a treatment for 1 hr/wk vs. receiving a single lecture as the control intervention, it is difficult to know whether any positive effect observed is due to the 1-hr weekly treatment or the effect on people’s attitudes from being in the clinic regularly. Ellenberg agreed that there is a way to account for these types of interventions, such as making sure that people are in the clinic for the same amount of time and receive the same attention. However, there are limits to which some aspects of treatment can be made similar.

Data mining, according to Ellenberg, is a tool for exploratory analysis. She believes it is fine to use available data to look for clues about the effects of different treatments or exposures, but care must be taken to interpret the findings cautiously. The danger is that people may think such analyses provide definitive results, but what is unmeasured might be what is causing the apparent treatment effects. Data mining can and should be used to generate new hypotheses.

A testing method that is gaining in popularity is the continuous process improvement (CPI) methodology, which is an unrandomized cohort study with a disease severity measure to substitute for randomization. Investigators engage in data mining to produce interesting hypotheses. It was asked what tests authors should use to determine whether findings are strong enough to justify the launch of a randomized clinical trial (RCT) and whether sensitivity analyses should be conducted when nonrandomized studies suggest biologically plausible hypotheses before such hypotheses are given serious consideration. Ellenberg believes that data mining can produce plausible results. Researchers must account for all of the known prognostic factors measured in the database and determine if there are important factors not measured in the database that can produce uncertainty. The result in a database analysis still needs to undergo further scrutiny because many biases are possible when analyzing databases looking for treatment effects.

In rehabilitation studies, the number of patients clinicians are working with would be outliers in RCTs performed in other fields. In RCTs, you need big populations to get normative data. This is a real challenge, perhaps especially for rehabilita-
tion. Ellenberg agreed that RCTs in rehabilitation may need additional design considerations to those of a placebo-controlled trial of a new drug agent, but good trials can still be accomplished. In reference to adaptive designs, it was asked if from a statistical standpoint there is any penalty for peeking at the data along the way. Ellenberg responded that if the designs are designed and carried out properly, they will maintain the probability of a type 1 error at the planned level. If interested in using this design it is necessary to meet with a statistician and understand the implications.

**BREAKOUT GROUP DISCUSSION AND RECOMMENDATIONS**

**Group 1: Musculoskeletal Spine Pain (Nontumor): Diagnosis and Treatment**

**Summary of Breakout Group Discussion**

With musculoskeletal spine pain, there is difficulty in determining where the pain is coming from and when identifying an area that is painful, it does not necessarily diagnose the pathophysiology. Because this is critical when making a decision about surgery, surgeons are more selective in determining when to operate. Despite this cautious approach, the rate of spinal fusions is rising dramatically.

An area yet to be explored is diagnostic manipulation and how it correlates with the magnetic resonance imaging data. There have been a number of studies that question using manipulation diagnostically. Presently there are no data to validate its use. Both diagnostic and therapeutic interventions are related issues when placing people in categories. The group questioned whether people can be placed in clinical categories that are testable or if the best that can be done is to categorize people for future diagnostic trials to determine who is right for what treatment. If a simple injection can stop pain and get people back to work, they asked whether it would be a valid therapeutic decision. Information is needed on the appropriate timing of interventions and for determining what treatments are reasonable and what evaluative criteria should be used.

Participants posed the question of whether there is value in primary prevention, which represents the onset of back pain. Perhaps more worthwhile is preventing disability and chronic pain. Or is advocating preventing disability a result of the advent of back pain?

The Human Genome Project may open a whole new area of research. It was felt that arthritis is still more an aging factor than a weight factor. The aging process is a major aspect of degenerative disease. This would argue that it is futile to think that we can prevent back pain. People don’t die directly of arthritis, but it has a great impact eco-

nomically for musculoskeletal problems since individuals live with this disability for 30 yrs.

The biggest predictor for an episode of back pain is the work that people do over a period of time. Identifying who is at risk and educating people in prevention is one step. Proper biomechanics can also help people to prevent occurrences of chronic problems such as carpal tunnel syndrome.

Factors also may be psychological. Researchers have tried for 30 yrs to predict who with back pain will become disabled. One priority is translational research. Age, body size, and previous back pain have lost currency as identifiable predictors and fixable factors. Instead, there may be hidden factors that have not been identified. More information is necessary to determine who is going to experience disability as a result of back pain.

Mutable factors are cognitive or behavioral in nature. Levels of depression, anxiety, and fear may change and these changes may impact chronic disability. Research needs to be done on coping skills to reduce the number of people who do not have physical problems, but are disabled.

Disability is legally defined more than 100 ways that include the inability to maintain gainful employment. As one ages, disability is defined as the inability to take care of oneself. For someone who is retired, a sedentary lifestyle may be adequate to take care of oneself. The psychosocial factor questions how people feel about their job and how important is it for them to be there. Trying to fix this with a medical solution is an enigma. It cannot be fixed at the bones and joint level? NIH may be interested in the cognitive areas as well. Research into brain function explores personality, which is a factor for people responding more appropriately.

Headliners for gaps in the research:

1. Biological level: where is the pain coming from?
   This is a foundation for further clinical trials
2. Why are some people disabled and others not?

Most work has been performed on the younger working population. However, older individuals with back pain are more likely to fall and use assistive devices. Older adults also have a steeper pathway to decline. Social aspects of back pain are different in the later decades of life. Back pain is relegated to the sideline when compared with heart disease and other life threatening conditions.

**Recommendations**

**Gaps in Knowledge**

- Can people with back and neck pain be divided into valid and reliable clinical categories to better target interventions?
- How can we prevent disability from chronic back and neck pain?
Can translational research explain and correct the fact that what we do know isn’t being used by both health care providers and patients?

How can we better understand the psychosocial causes of back pain disability and how can we modify them?

Define disability from back pain across the life span and ways to reduce it.

Optimal treatment of back pain in those older than 65 yrs of age.

What is the cost effectiveness of linking physical and vocational rehabilitation?

What are the components and intensity of the most effective rehabilitation interventions for chronic back and neck pain?

When and for which patients should invasive treatment be considered?

How does the clinician keep patients following a prescribed rehabilitation plan?

What is the pathophysiological etiology of back pain?

How is disability characterized throughout the decades of life?

Clinical trials are needed that use valid and reliable clinical categories

**Methodology**

- In outcomes research, look at cost and not just effectiveness. How much does it cost to get clinical improvement?
- Clinical trials should be done on subdivisions of back pain.
- All age groups need to be considered.
- Consider both quantitative and qualitative approaches to understand causative factors of disability from back and neck pain.

**Barriers**

- Lack of consistent subgroupings of patients: Classifications may vary between specific disciplines.
- A better integration of efforts of various professionals is needed so that each intervention optimally treats the full problem.
- Ineffective educational models both for patients and professionals must be addressed.

**Priorities**

- Can people with back and neck pain be divided into valid and reliable clinical categories to better target interventions?
- How can we prevent disability from chronic back and neck pain?
- Can translational research explain and correct the fact that what we do know isn’t being used by both health care providers and patients?
- A better understanding of the psychosocial causes of back pain disability and how we can modify them.

**Plenary Discussion**

Similarities between this group and the co-morbidity group were referenced because one of the biggest comorbidity components is back pain. It was asked if this group was satisfied with the existing outcome measures of disability for individuals with back or neck pain and if it was discussed as a methodological problem or barrier. Margolais responded that measuring back or neck pain isn’t the major issue; it’s the measurement of disability. More basic work needs to be done before back or neck outcome measures can be better identified. The group’s main concern was the psychosocial side of disability that has not been explored sufficiently.

In the comorbidity group, they struggled with recommendations for NIH review criteria, which traditionally are more pathophysiologic as opposed to looking at the whole person. Margolais was asked how his group dealt with the conflict between past priorities at NIH and the need to study the integrated patient. Margolis agreed that the holistic patient approach was also a priority and that patient-health professional communication must play a key role in the priorities to achieve a maximal result.

There was controversy over this group’s claim that elimination of pain is not the issue but rather the elimination of disability. The questioner believed that musculoskeletal problems reduce function as a result of pain. Margolais stated that disability occurs when a person decides he/she is disabled and disability and impairment are two distinct items and should not be thought of as the same. Impairment is the physical change; the disability is the effect on that person’s life and the ability to function. In the past the cause has been questioned, while there is a huge amount of disability that isn’t being attacked. Disability is in the head and not in the body, according to Margolais. There are no evidence-based materials to show this and he is asking for this to be recognized. It is necessary to find ways to assess the whole person. It is the opinion of this group that disability is a personal, psychosocial decision, based largely on the person’s attitude.

Magaziner took issue with the lack of distinction between a person’s attitude and a clinical definition of disability. Disability depends not only on a view of oneself, but also on one’s life experience.
Weinrich commented that there are vast complications in defining who is disabled. It depends not only on people’s view of themselves but also on their life history. Hazard commented that the definition of disability is becoming more confusing through the decades of life and in comparing employment issues with maintaining independence. In reference to the research on back and neck pain, disablement refers to external definitions of disability (legal or social), which are hard to measure and define. Little is known about how disability from back and neck pain affects older people.

There are currently 55 different federal definitions of disability. When discussing someone being disabled from the standpoint of employment, it further complicates the issue. The Social Security Administration’s definition of disability is that one cannot be employed at any job and make $800.00 per month.

Another commenter stated that many groups here struggled with the issue of the generic topic with respect to a specific disease or process entity. There is an important contribution to be made in developing disability measures that are targeted for physiologic or mechanical issues. There is a difference between pain and disability. Pain does not drive disability and disability does not always result in pain or dysfunction. Attention to detail about the nexus is a critical function and should be an important part of this group’s suggestion for outcomes.

**Group 2: Musculoskeletal (Nonspine) Pain: Diagnosis and Treatment**

This group believed that the first step in determining research priorities is a consensus conference to better inform everyone on the existing literature in the field, so they can then determine how to use what is available and what needs to be developed.

They discussed extensively pain as a means of diagnostic grouping and decided it was not an appropriate way to classify musculoskeletal conditions. It is a symptom as are other potential symptomatic presentations. There were also discussions about pain and disability and that there is no cure for all forms. With multiple priorities, the group decided to focus efforts at the top levels of the pyramid (impairment, functional limitation, disability and societal limitation).

**Recommendations**

**Gaps in Knowledge**

- Disease mechanisms of non-spine musculoskeletal pain:
  - Biomechanical—environmental factors and their potential predictive value at the impairment, functional limitation, and disability levels. This is a ripe area for tangible discoveries relevant to exercise, activity modification, shoe wear, and recommendations for physical modalities.
  - Potential mechanisms and predictive value of genetics and biochemical processes (nerve transmitters, neuro-hormones, hormones, cell receptors, and chemical milieu of painful tissues).
  - Better defined concept of anatomic and schematic maps of pain pathways in the body. It can be broken down into three parts:
    - Nerve or nervous system pathway
    - Connective tissue (muscle, joint, bone)
    - Visceral pain pathways.

**Methodological Issues**

- Definition of non-spine musculoskeletal pain
  - Etiology—define acute or chronic
- Indicators of pain
  - Diagnostics
  - Psychosocial
  - Environmental
- Multifunction assessment tools for non-spine musculoskeletal pain that can be used across the spectrum of clinical disciplines
  - Validated musculoskeletal physical examination that can be taught to research assistants.
  - Drive toward a mechanistic definition of pain using quantitative sensory testing that can be done in a clinical setting
  - The tools should be multidimensional, standardized, and transdisciplinary
  - The tools should include psychosocial and multicultural factors
- A small set of “red flags” to rule out a disorder such as cancer or an infection that can be disseminated as a guideline

**Priorities**

- Identify treatment effectiveness through:
  - Understanding the association between pain and function to better understand how interventions may improve a situation
  - Identifying interventions for reducing pain from fracture to visceral pain
  - Identifying interventions to increase function and decrease disability, despite pain
- Algorithms for treatment guidelines, which must be evidence-based and incorporate a meta-analysis or an annotated bibliography
- A consensus conference on musculoskeletal pain issues. Many topics could be addressed within...
this meeting that need validation and testing for reliability

**Plenary Discussion**

In the comorbidity group, according to a participant in that group, they struggled with the need to understand the normal to help with handling the abnormal. The conference is focusing on rehabilitation, but there is the need for insight to know what to do with people with impairments. This group was reticent to jump completely into biomechanics, but the thought process was to develop normative scales in biomechanics, to include the level of strength and force production.

One commentator would like to see more on mechanisms in this priority. For example, she was intrigued by the paper on fibromyalgia and the role of hypersensitivity. She wondered to what extent sleep disorganization alters the pain sensitivity threshold. The group felt that they tried to capture that in the potential mechanisms and predictive value. One of the areas that they covered in their discussion was the effect of a heat modality on what they are trying to treat. On a more basic level, related to priorities 1 and 2, they discussed how to measure these treatments.

The real value of overuse syndrome from a biomechanical standpoint should be explored to better understand why some people react to a thousand repetitions in such different ways from others. Researchers in the 1930s struggled with the same issues when analyzing workers on an assembly line. They came up with a robust model and a diagram that may be just as valid today. It included what was task related, what was related to the workers' personal histories, what was objective, and what was subjective.

**Group 3: Postsurgical Management for Orthopedic Conditions**

This group centered on five target conditions for recommendations and priorities. They are hip fracture, multiple trauma, rotator cuff, amputation, and elective total joint replacement. In general, the gaps in knowledge related to frequency, intensity, and duration of specific interventions and therapeutic exercises and how they relate to functional activities.

Issues that differed from other groups included under hip fracture: the development of reliable and valid technologies to capture biomechanical factors in vivo and in clinical practice; and seemingly "risky" clinical trials to challenge common wisdom. This issue questions how to conduct a clinical trial when denying someone a certain level of care. This group also questioned whether there was clear clinical criteria for decisions made for surgical management through to rehabilitation management, or if it is left to the clinician. They also asked what study designs are available to help in that decision making. With scarce dollars a major issue in rehabilitation funding is whether it is worthwhile to develop measures that titrate the dose-response relationship between rehabilitation and function.

Thematically, in the group's work, were criteria for clinical decisions or indicators. They discussed weight bearing in particular and how to know when it's time to move to the next step. Although presently this is based on clinical intuition, common wisdom and training, it requires more scientific data.

In discussing amputation, they spent much time on the re-emergence of traumatic war injury. This is re-establishing a new area of research and how an ugly mine wound differs from other forms of amputation. This also raises concerns about motivational factors, and patient acceptance and expectations for self-image and social function. Methodologically, this is not an area that is easy to find matched controls for any given set of clinical characteristics. There is a question regarding whether there are appropriate functional measurement instruments in this population. There is also slow dissemination of prototypes for prosthetic devices for widespread clinical practice related to expense of devices.

**Hip Fracture**

**Gaps in Knowledge**

- Thresholds in pathology and healing that impact rehabilitation progression, including criteria for weight-bearing activity.
- Pain control that facilitates rehabilitation.
- Frequency, intensity, and duration of specific therapeutic exercises to accomplish certain functional activities.
- Selection and timing of interventions across time and settings based on recovery process.
- Secondary prevention of contractures.
- Overall optimal strategy to enhance mobility.

**Psychosocial Issues**

- Self-efficacy
- Impact of caregiver availability
- Motivation to recover
- Impact of cognitive impairment on recovery

**Emerging Scientific and Translational Issues**

- Development of reliable and valid technologies to capture biomechanical factors in vivo and in clinical practice
Methodological Issues

- Seemingly “risky” clinical trials to challenge common wisdom
- Alternative study designs to describe criteria for clinical decisions
- Expansion of definitions of “mobility” to include community participation
- Sensitivity of measures that could titrate the dose-response relationship between rehabilitation and function
- “Function” as an individualistic notion is not always equivalent to research-defined “function” or normatively-determined “disability”

Specific Barriers

- Time and funding to balance clinical practice and research priorities
- The “research” episode of care is lengthier than the “reimbursable” episode

Research Priorities

- Criteria for stability fixation and weight-bearing activities
- Strategies to return individuals to premorbid level of function and augmented capacity for an expanded reserve and an enhanced quality of life
- Prevention of secondary complications including loss of muscle mass
- Identification of indicators predicts rehabilitation potential and readiness to progress

Level of Research Outcomes

- Pain (acute pathology); Impairment; Functional Limitations; Disability

Rotator Cuff; Degenerative Soft-Tissue/Ligamentous Repair

Gaps in Knowledge

- Relationship between and among multiple joint problems and other kinds of impairments that alter load and stress tissues abnormally.
- Criteria for early detection and appropriate referral for presurgical rehabilitation.
- Timing for initiation of postsurgical rehabilitation.
- Techniques that enhance recovery specific to characteristics of the lesion
- Specific risk factors for rotator cuff injury
- Quantification of effective rehabilitation programs beyond the “black box”

Psychosocial issues

- Emerging scientific and translational issues:
  - Imprecise diagnostic technologies and validity of findings
  - Underutilization of motion analysis techniques incorporating scapulothoracic and glenohumeral movements and specific muscle activation to accomplish functional activities

Methodological Issues

- Nonspecific use of “physical therapy” or “operational therapy” as the description of the intervention without further details that would allow replication of the study or exploration of dose-response relationships

Specific Barriers

- Rehabilitation outcomes research does not easily fit into orientation of funding

Research Priorities

- Quantification of rehabilitation interventions and dose-response relationships to achieve specified outcomes

Level of Research Outcomes

- Impairment; Functional Limit

Amputation

Gaps in Knowledge

- Match among residual limb characteristics, patient perspectives and functional needs
- Cost-effectiveness of available and emergent technology that benefits both individual and society
- Impact of amputation on other anatomical and physiologic systems
- Impact of the mechanism of injury on criteria for surgical decisions and rehabilitation prognosis as well as rehabilitation program
Psychosocial Issues
- Attitudes and motivational factors that impact rehabilitation process and influence expectations for prosthetic technology
- Device acceptability relative to patient-specific criteria for self-image and social function

Emerging Scientific and Translational Issues
- Impact of variable geometry sockets on secondary complications

Methodological Issues
- Finding matched controls for any given set of clinical characteristics
- Development of appropriate functional measurement instruments

Specific Barriers
- Slow dissemination of prototypes into clinical practice

Research Priorities
- Criteria for matching individual to device and device to desired function
- Differences in functional outcomes across devices

Level of Research Outcomes
- Pathology, Impairment, Functional Limitations, Disability

Elective Total Joint Replacement

Gaps in Knowledge
- Timing, intensity and duration of rehabilitation
- Effectiveness and appropriateness of therapeutic exercise and therapeutic activity
- Impact of unilateral vs. bilateral replacement on functional progression and duration of the episode of care
- Justification for variations in care across settings and criteria for matching patient needs with service delivery
- Impact of setting on outcomes including access, availability, and coordination of multidisciplinary services
- Optimization of pathways that allow for recurrent or nonlinear variations in intensity to respond to patient needs
- Impact of pre-existing neurological disorders, systemic arthritis, or other musculoskeletal problems on functional recovery and rehabilitation

Psychosocial Issues
- Impact of joint replacement on work

Emerging Scientific and Translational Issues
- Impact of minimally invasive techniques on functional recovery and episode of care
- Applicability of animal and simulation models to identifying “best” practice
- Relevance of science to policy development (does data have anything to do with it when decisions are driven by economics)

Methodological Issues
- Appropriateness of other study designs when RCTs are not practical or possible

Specific Barriers
- Limitations in scientific appreciation and “early buy-in” by policy-making stakeholders
- Investigations of cost-effectiveness and appropriateness of care do not easily fall into funding priorities

Research Priorities
- Policy-relevant outcomes: independent living potential; return to work potential; long term impact on medical and health costs

Level of Research Outcomes
- Pathology, Impairment, Functional Limitations, Disability

Multiple Trauma

Gaps in Knowledge
- Long-term outcomes of reconstructive surgery
- Long-term needs for rehabilitation over the life span
- Impact of multiple-extremity involvement on rehabilitation process and episode of care
- Impact of multiple comorbidity
- Criteria for rehabilitation decisions beyond acute needs or immediate clinical presentation
- Natural history of functional recovery in this population
- Impact of muscle fibrosis on long term function

Psychosocial Issues
- Risk-taking behaviors and prevention
- Chronic pain and depression
Economic productivity and employment opportunities over the life span

Emerging Scientific and Translational Issues
- Impact of new technologies oriented toward pathologies and tissue regeneration to accelerate rehabilitation process

Methodological Issues
- Longitudinal study designs that capture data relevant to systems planning

Specific Barriers
- Identification of specific clinical cohorts

Research Priorities
- Observational studies of functional recovery and rehabilitation over the long term

Levels of Research Outcomes
- Pathology, Impairment, Functional Limitation, Disability

Plenary Discussion
In reference to the risk of clinical trials, Weinrich suggested that there also is a risk to not performing them. Referring to a clinical trial done on laproscopic lavage for OA of the knee, he indicated that although 100,000 were conducted each year before the trial, the study showed the procedure had no benefit. This discontinuation avoided not only expense, but the morbidity and mortality of a surgery that everyone thought was efficacious before the trial proved otherwise.

A participant noted that, on the last topic, there were not other comorbidities listed, such as brain injury and spinal cord injury that should be added in a trauma patient. Although the group recognized that they exist and have impact, they expected it to be covered somewhere else.

Group 4: Severe Deconditioning
There is no universal agreement as to the meaning of the term “deconditioning,” but several components of a definition were identified by the group.

Deconditioning
- It is manifested as fatigue (as reported by the patient)
- It is in response to some degree of exertion
- It includes the inability to perform at a given level

Gaps in Knowledge/Opportunities for Research
- The reasons for the variability in the response to the cause of deconditioning are unknown
- The association with physical activity must be experimentally tested
- Optimal interventions must be defined
- The windows for interventions at different stages of the process should be identified
- Markers for responders and nonresponders (to deconditioning and to interventions) are needed
- Response to reconditioning interventions in different chronic illnesses must be studied
- A combination of potential interventions including hormonal and nutritional treatments should be developed
- Meaningful (functional) outcomes must be identified and used consistently across studies
- Noninvasive techniques to study skeletal muscle must be developed

Psychosocial Issues
- The role of psychosocial factors in deconditioning must be defined, including the relationships between education, economic level and physical activity.
- The effect of psychosocial factors on motivation to exercise and compliance remain to be defined.
- Environmental determinants of level of physical activity should be identified.
- Racial and ethnic differences in response to deconditioning may explain some of the variability in responses.
- Social mechanisms that may foster exercise habits are needed.
- Perception and knowledge of fatigue by patient, health care providers, and society must be understood because not all define fatigue the same way.
- Addictive nature of inactivity must be addressed.

Emerging Scientific and Translational Issues
- Understanding muscle deconditioning and reconditioning at the molecular and cellular levels
- Understanding fundamental molecular and cellular controllers of muscle atrophy and respective pathways
- Developing technology to measure changes in skeletal muscle (may include new imaging techniques)
- Defining the role of mitochondrial dysfunction and developing new technology to measure it
- Studying the capacity for muscle regeneration in the context of advances in (stem cell and satellite cell research)
- Studying other factors that may block or facilitate reconditioning, such as drugs for various medical conditions.
- Effectively translating our knowledge into effective public health recommendations we need to understand how to get people active!

**Methodological Issues**

- The diagnosis of deconditioning is not easy and there are no universally acceptable criteria. Thus, it is difficult to establish the its prevalence.
- It would be of interest to separate the pathology that affects skeletal muscle from the deleterious effects of physical inactivity.
- Our ability to measuring physical activity level in different populations using GPS technology and/or accelerometers must be enhanced.
- The technology to measure muscle function and structure is insufficient.
- If we develop a working framework for studying fatigue and an acceptable definition, it will be easier to measure.
- Measurements of function and meaningful clinical outcomes deserves significant attention. Given the difficulties in studying deconditioning in rehabilitation, it may be necessary to develop a clinical trials network and statistical approaches other than the standard.

**Specific Barriers**

- High cost of RCTs
- Deconditioning trials may be of no interest to many drug companies
- Heterogeneity of the population to be studied
- Hospital culture (impact of deconditioning not perceived by staff)
- Lack of evidence leads to too much individualization in the design and implementation of treatment and rehabilitative interventions
- Difficulty in defining the intervention
- How to make the diagnosis?

**Research Priorities (in Order)**

- Develop criteria to diagnose deconditioning, establish prevalence, dissect the pathology
- Study the mechanisms and pathophysiology (in different diseases), i.e., controllers of muscle atrophy
- Interventions to correct deconditioning, i.e., the importance of maintaining a habitual level of physical activity, the development of specific interventions, and the establishment of meaningful outcomes
- The development of technology to study muscle and person activities

**Levels of Research Outcomes**

- All levels of the model
- Improve patient function (mobility, independence) and community reintegration
- Increase scientific knowledge
- Patient centered

**Plenary Discussion**

In an ICDR compendium of federally funded assistive-technology research, the category for recreation and exercise has the least amount of funding of any other project area, despite the importance of exercise. NIDRR is now funding a Research Engineering Research Center on exercise for people with disabilities and there has been talk at interagency meetings about using the Small Business Innovative Research mechanism to develop accessible equipment for greater safety. This important issue might be addressed through announcements by the Small Business Innovative Research or through tapping another mechanism. An underlying assumption of this group is that the prevalence of deconditioning is very high in the general population and in nursing homes; even though there is abundant evidence that exercise is a safe and effective intervention.

In the part on mechanisms, a suggestion was made to include biomechanics in the area involving discovery. At the cellular level they are focused on deconditioning and reconditioning and there may be areas of importance at the biomechanical level, such as a key muscle group to strengthen. Functional as well as physically active should be included in the goal. Biomechanics will target the intervention in a more functional way.

When talking about patient compliance, patient advocacy groups have taught it is a physician-specific term and a more appropriate way to phrase it is “patient values,” rather than “physician centric.” Clinicians should think of patients as part-
ners in creating exercise and diet programs that work for them.

Another comment addressed adding the degree to which behavior modification influences interventions and effects recovery from deconditioning, particularly as it impacts fear of injury or reinjury.

**Group 5: Musculoskeletal Problems as Comorbidities**

Musculoskeletal problems as comorbidities are a huge issue epidemiologically and exact a significant burden on patients, their families, and the healthcare system. Two major population trends will be making these issues much more prevalent in the future—survival into later years of many people aging with disabilities and the aging of the general population.

The breadth of the discussion reflected the many disciplines, perspectives, and organizations represented by participants. The initial approach in the working paper, “Musculoskeletal Problems as Comorbidities,” by Hilary Siebens, was uniformly felt to be a helpful start. Subsequent discussion on day 1 touched on numerous dimensions and initial research ideas. Two issues challenged the group. First, the breadth of the topic was enormous. It could include both musculoskeletal components of patients’ specific health conditions/diseases and patients’ musculoskeletal problems that were unrelated to their other health conditions. Second, although high priority issues were identified for NIH research, it was acknowledged that other related areas were important and advocacy by other research funding agencies could also help move the research forward.

On day 2, the key areas for research were organized into 10 thematic areas:

1. Methodology—diagnosis, measurement, approach to research
2. Etiology—predisposing, preclinical, progression, risk factors, complications, mechanisms
3. Prevention/treatment/holistic approach
4. Adaptations—positive, negative
5. Influences on medical management—of other diseases, conditions
6. Patient-provider
7. Lifespan
8. Psychological considerations
9. Social, cultural, environmental
10. Healthcare system/policy

Important characteristics of musculoskeletal comorbidities, clinical issues, and research topics were covered in most areas.

One participant suggested that the entire subject area may benefit from a formal NIH consensus conference. Such conferences would include additional work in assessing the knowledge base and specific research needs.

**Recommendations**

**Gaps in Knowledge**

- Bi-directional interactions of other diseases and conditions that lead to musculoskeletal issues
- Disease progression
- Making of diagnoses and issues by other diseases/conditions
- Exacerbations of other diseases/conditions and their effects on musculoskeletal problems and visa versa
- Variability in outcomes
- Windows of opportunity to diagnose and intervene for best results

**Methodological Issues**

- Better definitions
- Better measures
  - Laboratory
  - Clinical
  - Community-based
- Inclusion of understudied groups

**Psychosocial Issues**

- Adaptation (positive and negative) by patients and providers
- Concordance of patient-provider priorities needs further evaluation—issues include negotiation, patient-centered care, empowerment, self-management
- Influence of spirituality, resilience and other factors on outcomes

**Barriers**

- Dynamic waxing and waning nature of musculoskeletal comorbidities
- Delays in diagnosis of musculoskeletal issues
- Disparities in access to health care and cultural attitudes

**Priorities**

- Multidisciplinary care coordination
- Holistic approaches to address multiple morbidities and complexity
- Appropriate points of entry to health care for patients with musculoskeletal conditions
Final Notes

The ICDR public Website (www.icdr.us) has a file with all the federal definitions on disability. Many groups commented on cultural issues and cultural sensitivities.

The Center for International Rehabilitation Research Information Exchange (CIRRIE), http://cirric.buffalo.edu/, has a series of ten monographs on the most prevalent cultural groups in the United States and the factors most indigenous to those groups that may impact on rehabilitation.

REFERENCE

Musculoskeletal Rehabilitation
Current Understandings and Future Directions

ABSTRACT


This work examines the current state of knowledge regarding the efficacy of rehabilitation for patients with major lower-extremity joint replacements, hip fractures, and amputations. Of particular focus is the use of inpatient rehabilitation strategies for functional restoration. These areas of rehabilitation involve common conditions in the elderly population. Cost-containment pressures have highlighted the focus on the efficacy of inpatient rehabilitation for persons with joint replacements in particular. Medicare’s “75% rule” specifically limits persons with elective joint replacements from entering rehabilitation units after their surgeries. This article highlights research relevant to these issues and was written to examine the state of knowledge about these topics with the goal of highlighting areas that need more research attention.

Key Words: Joint Replacement, Hip Fracture, Amputation

Rehabilitation services commonly are used for persons with a variety of musculoskeletal disorders. Persons with degenerative or rheumatoid arthritis undergoing elective surgery to replace diseased lower-limb joints require rehabilitation services to achieve optimal function. Emergent joint replacements and operative fixation for persons sustaining hip and femur fractures, particularly for osteoporotic and frail elderly persons, must be followed by remobilization and rehabilitation. Persons who incur a lower-limb amputation as the result of trauma or peripheral vascular causes require prosthetic devices, pain control, and functional restoration.

Rehabilitation services today are provided at comprehensive inpatient rehabilitation units attached to acute-care hospitals or free-standing rehabilitation hospitals. Less-intensive rehabilitative services also are administered in skilled nursing facilities, at outpatient rehabilitation facilities, or at home through home health care.

Against this backdrop of the need for rehabilitation services for these patients, Medicare is implementing a phased in “75% Rule” that mandates that 75% of patients on a comprehensive inpatient rehabilitation unit carry one of the core diagnoses as the reason prompting admission. This has in effect, forced rehabilitation units to reduce, or curtail altogether, admissions for patients with...
unilateral knee or hip replacements. Patients with amputations, however, are included within these accepted diagnostic categories. This cost-containment measure has raised concern among rehabilitation professionals as a policy that effectively limits access to rehabilitative care for some patients.

It would be optimal if the efficacy and outcomes of rehabilitation care were well-known and widely accepted with strong rationale for the many interventions. Unfortunately, our science is not sufficiently developed in some areas for us to make definitive statements regarding the proper venue for rehabilitation and the intensity and content of services that constitute the best care for most musculoskeletal conditions. The purpose of this article is to bring together current knowledge regarding rehabilitation care for persons with hip fractures, knee and hip replacements, and amputations with a specific focus on the post acute rehabilitation care needs.

Assessment of the Literature

Using the MEDLINE search engine to examine the National Library of Medicine citations, we examined the literature using appropriate key words and multiple different search strategies. Randomized trials were examined as well as cohort studies, particularly large-scale prospective cohort studies examining meaningful outcomes.

Rehabilitation for Persons with Hip Fractures

Hip fractures often are a devastating injury that occurs for the most part in elderly osteoporotic women but also in men. These persons are treated with operative fixation of the fracture using a total hip replacement or other operative procedure that allows early mobilization and ambulation. Other complications of immobility, such as venous thromboembolism, decubitus ulcers, and weakness, can occur in this high-risk group.

A prospective cohort multicenter study across 17 different states assessed the outcomes and costs after hip fractures and stroke. In this study, a total of 500 randomly selected patients with hip fractures and 485 stroke patients were examined 6 mos after incident admission. This important study showed that stroke patients admitted to rehabilitation hospitals were more likely to return to the community and recover their function than if they were sent to a nursing home. However, with respect to hip fracture patients, inpatient rehabilitation did not differ from nursing home care when analyzing return to community or activity of daily living improvements. Although not a randomized trial, this large study representing 92 rehabilitation facilities and skilled nursing facilities encompassing 17 states included a wide range of patients with excellent generalizeability to other populations. Case mix adjustments, always an issue with non-randomized studies, tempers the strength of these results.

A study by Stramberg et al. involved an intervention regarding orientation and mental awareness using a clock, calendar, and television set for persons with hip fractures. The intervention group received these interventions and a control group did not. The short mental status questionnaire served as the primary outcome measure. There were no significant differences in mental status across the two groups. However, the most compelling finding was that 13% of both groups deteriorated mentally between admission and post-operative evaluation.

A particularly interesting study was published by Ottenbacher et al. that examined the relationships between declining lengths of stay in rehabilitation and functional outcomes and mortality from 1994 to 2001. These investigators sought to understand the relationship between decreasing lengths of stay and the functional consequences for patients undergoing rehabilitation. This retrospective cohort study included patients for whom information was submitted to the Uniformed Data System for Medical Rehabilitation. This very large study analyzed data from 744 inpatient rehabilitation hospitals in 48 states. A total of 448,807 patient records from five impairment groups (stroke, brain dysfunction, spinal cord dysfunction, other neurological conditions, and orthopedic conditions) were examined. These investigators found that the lengths of stay for medical rehabilitation significantly and substantially decreased for all five impairment groups. However, there were no decrements in activities of daily living, indicating that greater efficiencies in rehabilitation occurred to maintain these gains. Of note, persons with orthopedic conditions had a significant (P = 0.0003) increase in mortality during this period of time. Although a strong study, this investigation did not include patients who were not admitted to hospitals participating in the uniform data system. These investigators used multivariate statistics to control for severity and case mix variables. This study raises concerns for the negative impact on mortality of declining lengths of rehabilitation stay.

In a companion editorial, Esselman raises several lucent issues. Dr. Esselman points out that, during this period of time, many rehabilitation programs expanded interdisciplinary rehabilitation services from 5 to 7 days/wk (e.g., weekend therapies), which may have improved the rehabilitation efficiency. The high scrutiny of managed care insurers promoting goal-oriented rehabilitation may have forced greater efficiencies. Wider implementation of and adherence to clinical pathways may
explain some of the greater efficiencies. Dr. Esselman points out that the impact of the 75% rule will result in reducing the number of patients with joint replacements admitted to an inpatient rehabilitation setting and will likely increase discharges to nursing homes or home care. The effect of the 75% rule on mortality should be further assessed.

The field of physical medicine and rehabilitation is broad and expansive yet suffers from a notable deficiency in health services research. Large-scale studies similar to that conducted by Ottenbacher et al.3 are vital for our field to understand rapidly changing health care trends and their influences on care delivery. Very little is known about the distribution of patients receiving rehabilitation services, and even less is understood about the long-term outcomes of these patients receiving services in different settings. This area is one that should be targeted for additional funding in the future. Of particular concern is our inability as a field to respond to rapid changes in the health care environment. This study by Ottenbacher et al.3 indicates that the increased mortality across diagnostic groups were associated with length of stay declines. Development of health services research centers that provide more real-time analyses to chart changes in policies would inform health policy advocates enabling more educated arguments about the impacts of newer policies.

Studies such as those undertaken by Kramer et al.4 involving large prospective cohorts with sophisticated multivariable analysis techniques, although not as powerful or definitive as randomized controlled trials, have many benefits for rehabilitation. For persons with spinal injuries and brain injuries, it is difficult to structure a randomized trial regarding rehabilitation outcomes in different care settings. For persons with orthopedic disorders, this is somewhat easier. A body of literature that includes prospective cohorts could shed considerable light on the more fundamental issues confronting rehabilitation scientists, that is, the effectiveness of our care and the most appropriate care setting. This discussion is not meant to criticize the vital role of randomized controlled trials. However, the difficulty with such trials in rehabilitation-based populations deserves special mention.

Huusko et al.5 compared specialized geriatric care with standard hospital care for persons with hip fractures after surgical care. In this study, 248 independently living patients ages 65 or older were randomized to one of two groups. The intervention group was referred to a geriatric unit specialized in rehabilitation that included twice-daily physiotherapy and daily activities along with more intense nursing care and common rehabilitation interventions such as drug treatment, occupational therapy, and speech therapy, as well as equipment and daily living aid training. The control group was discharged to a general hospital and treated by primary care physicians. The outcomes were measured in terms of length of stay and independent living after 3 and 12 mos. Two subgroups were evaluated; those with mild dementia and those with severe dementia. The outcomes were significant in favor of the intervention group. For persons with severe dementia, the intervention group was much more likely to be independently living after 3 mos (63% in the intervention group compared with 17% for the control group). Independent living after 1 yr was 62% in the treatment group compared with 33% in the control group. With respect to persons with mild dementia, those who went to the geriatric rehabilitation center were more likely to be independent living after 3 mos (91% compared with 67%). However, at 1 yr there were no differences in independent living (77 vs. 76%) for the mild dementia group. The mean lengths of stay for hospitalization were significantly reduced in the intervention group compared with the control group.

Delirium is an unfortunate secondary condition that can occur after a hip fracture and the corrective surgery. A randomized trial investigated the usefulness of daily consultative visits from a geriatrician.6 This consultation addressed many of the issues related to acute delirium, such as medication assessment, electrolyte management, and nutritional intake. This intervention demonstrated a significant and meaningful reduction in delirium, 32% in the intervention compared with 50% for the usual care group. Severe delirium was noted in 12% of the treatment group and 29% of the usual care group. These authors concluded that proactive geriatrics consultation reduced delirium in persons with a hip fracture.7

In another randomized trial, Naglie et al.7 studied patients with hip fractures and randomized them to either an inpatient rehabilitation program or standard care received on a general ward. The study population consisted of 279 patients older than the age of 70 who underwent surgical repair for hip fracture. Outcomes included ambulation and transfer ability as well as mortality rates. The intervention consisted of interdisciplinary ward care with protocols and standardized orders to prevent problems in these patients such as pressure ulcers, venous thromboembolism, and pain. Twice-daily physiotherapy sessions 5 days/wk were held. At 6 mos, there were no differences in ambulation or transfer abilities. Multiple logistic regression analyses showed no significant differences between the treatment groups for all outcome measures.

Twelve-month outcomes for patients with hip fracture who were randomized to either an early discharge and home based therapy or hospital
based rehabilitation have been reported. There were 34 and 32 patients in these groups, respectively. The participants in the treatment group were discharged within 48 hrs of randomization and were visited at the home by physiotherapists, occupational therapists, speech pathologists, and therapy aids. The intensity of care given by these home-based treatments was unclear. Patients in the hospital group were given standard inpatient rehabilitation care. At 1 yr after discharge, there were no differences in the modified Barthel Index scores or SF-36 scores. The investigators concluded that an early discharge and a home rehabilitation program did not adversely affect patient outcomes. Tinetti et al. in a similar type of randomized comparison of standard home care and an augmented home therapy program, found no differences in 6- and 12-mo outcomes.

One study involved randomizing patients with hip fracture to either a home-based program or an inpatient rehabilitation program. In this study, 31 patients were recruited and randomly assigned to a home group, receiving five home physiotherapy visits and two community nursing visits. The other half were assigned to a control group who went to an inpatient rehabilitation hospital. The outcomes in terms of ambulation were no different between the home-based group and the inpatient rehabilitation group.

A randomized trial conducted in Stuttgart, Germany, compared the efficacy of institutional rehabilitation after surgical treatment of hip fractures to outcomes for persons discharged directly home. Six-month and 1-yr outcomes demonstrated no significant benefits of inpatient rehabilitation with respect to mortality and functional improvement over a home care program.

Hedstrom et al. found that anabolic steroids in moderate doses along with a vitamin D and calcium can minimize the deleterious effects on musculoskeletal system for persons post hip fracture. Such treatment can prevent loss of muscle mass and, surprisingly, improve gait speed significantly.

Medicare claims for 29,793 Medicare service beneficiaries who completed treatment in 1996 and 1997 in rehabilitation facilities that subscribed to the uniformed data system for medical rehabilitation were analyzed. In particular, the change in motor FIM scores for persons with hip fracture was no different across treatment sites. As the authors pointed out, however, only 60% of the inpatient rehabilitation facilities in the United States, and only 11–25% of skilled nursing facilities provide information to the Uniformed Data System for Medical Rehabilitation. These authors further pointed out we have yet to determine what is more important, where the patient received care or the type and intensity of care received. Subacute rehabilitation facilities were thought to provide less costly care with essentially the same outcomes as those provided in an inpatient rehabilitation facility for persons with hip fractures.

**Elective Joint Replacement**

Postoperative care needs for persons undergoing elective joint replacements has received considerable research attention. This is a particularly important topic in light of recent Medicare rules regarding the “75% rule,” which effectively limits some persons with elective joint replacements from entering the rehabilitation service. The overall findings from a number of studies described below suggest that less intense postoperative rehabilitation is as effective as inpatient rehabilitation for most patients.

One study in Denmark evaluated the effectiveness of a joint-recovery program. In this trial, the results of a joint-recovery program were compared with standard care. The joint-recovery program consisted of preoperative counseling, functional evaluation, and home care needs assessment and implementation. Postoperatively, the patients were given more intense physiotherapy. The outcomes were compared with a group who only had postoperative physical therapy. The results demonstrated reductions in mean length of stay for total hip replacement patients (43% reduction in the treatment group). A 58% reduction in total length of stay for persons with knee replacements was noted. Of particular note were the cost savings. For persons with total hip replacements, $1261 was saved per case and for persons undergoing knee replacements, $3336 was saved per case.

Postoperative rehabilitation for persons undergoing elective knee and hip arthroplasties was examined by Munin et al. They compared an early rehabilitation program beginning on postoperative day 3 to one starting on the seventh postoperative day. In this inpatient rehabilitation program, earlier intervention led to shorter lengths of stay and more rapid attainment of functional milestones between days 6 and 10. This study showed that an earlier intense rehabilitation was better than a rehabilitation intervention started a week after the operation.

Mitchell et al. examined costs and effectiveness of pre- and postoperative home physiotherapy for total knee replacement. The intervention group received preoperative physical therapy and pain relief techniques as well exercises to increase knee flexion and extension. In addition, postoperative physiotherapy included techniques to reduce soft-tissue stiffness and increase range of motion. This preoperative and postoperative care was compared with the control group, which only received the...
usual hospital physiotherapy before discharge. In this randomized trial, there were no significant differences in quality-of-life outcome measures or mobility. However, the preoperative physiotherapy group was significantly more costly than standard therapy. It was concluded that the preoperative therapy provided no additional benefit and was more costly.

In contrast, another randomized controlled trial assessed a longer course of preoperative exercises for persons undergoing total hip arthroplasties. Intervention arm subjects had 8 wks of preoperative exercises and the controls did not. Outcome measures included a 6-min walk test. The intervention group demonstrated greater gait velocity at 3 wks after surgery. At 12 and 24 wks after surgery, gait velocities were greater and distances on the 6-min walking tests were significantly increased in the preoperative group.

In a randomized controlled trial, home care was compared with inpatient hospital care for persons with hip joint replacements. In terms of SF-36 and physical functioning, the 3-mo outcomes were the same across groups. These authors concluded that the cost of hospital care becomes a primary concern when treatment at home and hospital have similar outcomes.

Kramer et al. studied the effects of a 12-wk supervised exercise program for persons after total knee arthroplasty and found that this prolonged exercise appeared to improve ambulatory ability over control subjects who did not receive such care. Other investigators have found similar modest benefits of a more intense exercise program for post joint replacement patients.

Sufficient pain control after joint replacement to facilitate inpatient rehabilitation was found to be an important aspect of such care. In a randomized controlled trial, 59 patients admitted for inpatient rehabilitation after total knee arthroplasty were randomized to receive controlled release oxycodone (oxycontin) every 12 hrs on a scheduled dosing regimen or placebo, in addition to the immediate-release oxycodone given to both groups on an as-needed basis. Compared with the placebo group, the patients who received oxycodine reported significantly less pain and achieved significantly greater knee motion and improved quadriceps strength by the eighth physical therapy session. Patients with pain control from oxycodine also were discharged from the rehabilitation unit on average, 2.3 days earlier than patients receiving placebo. This study illustrates the value of optimal pain control for rapid functional restoration.

Various types of specialized exercise equipment and techniques have been examined with no clear benefits over standard physical therapy demonstrated. Occupational therapy and other outpatient care mechanisms can speed attainment of improvements in activities of daily living in the short term, but this care affords no long-term benefits.

Salmon calcitonin nasal spray has been shown to improve the clinical outcome of postmenopausal women after total hip arthroplasty. Harwood et al. showed that vitamin D supplementation using vitamin D can reduce the rate of falling by 50%. Supplemental tube feeding via nasal gastric tube or other means of additional nutrition for elderly women with a femur fracture showed benefits in terms of improved anthropomorphic measurement as well reductions in the time taken to achieve independent mobility. These effects were most pronounced in the very thin group of elderly females. Such findings can provide the foundation upon which sound evidence-based care guidelines are implemented for patients.

Rehabilitation of Persons with Amputations

The complete or partial loss of a lower limb often occurs in older persons with underlying peripheral vascular disease or diabetes. Other causes of limb loss or deficiency trauma-related amputations, those resulting from limb malignancies, and those secondary to congenital anomalies occur far less frequently. An investigation using national Hospital Cost and Utilization Project data demonstrated that the rates of lower-limb amputations as the result of peripheral vascular disease and diabetes have increased by 27% in the United States from 1988 to 1996. In contrast to dysvascular amputations, limb amputations caused by trauma and cancer significantly declined by 50 and 43%, respectively, during the same period. Among persons with diabetes, African Americans, Hispanics, and Native Americans are at much greater risk for lower-limb loss than white persons.

Maryland hospital discharge data were used to examine the epidemiology of amputations secondary to peripheral vascular disease from 1986 to 1997. Incidence rates for dysvascular amputations increased from 41.4 per 100,000 in 1986 to 47.2 per 100,000 in 1997. For all levels of amputation, annual incidence rates among African-American subjects were considerably greater than those of other persons. African-American patients were two- to fourfold more likely to lose a lower limb than white persons of similar age and gender. The excess morbidity caused by limb loss is profound in minority communities and warrants investigations into their prevention through public health policies and initiatives.

Postoperative wound care is a vital aspect for maintaining an optimal healing environment. Soft bandages cover a wound effectively and pro-
vide accommodations for surgical drains. However, these bandages have been associated with edema formation and, when not properly applied, can “choke” the end of the residual limb, resulting in excessive edema and a more bulbous end, which places the wound at risk for dehiscence and breakdown at the surgical margins. One mechanism for addressing these problems with soft dressings is the use of rigid cast dressings placed on the residual limb immediately after surgery.53–56

In one study of 154 patients randomized to either soft dressings or immediate cast dressings, no advantages to this intervention were found in terms of time to prosthetic casting or postoperative infection rates.56 In contrast, Wong and Edelstein55 found that Unna semirigid dressings applied a month after surgery in a small sample of 24 patients (12 in the Unna group and 12 in the soft-dressing group) were more effective in promoting wound healing and significantly shortened the time to prosthetic ambulation.

Malone57 found that early fitting with a prosthesis immediately after amputation for upper-limb amputees resulted in better acceptance of prosthetic devices. Malone felt that fitting early was critical to an amputee’s success.

For patients with lower-limb amputations caused by trauma, the vast majority (98%) successfully use prosthetic devices and do so many hours of the day.58 The majority of dysvascular amputees with transtibial amputations successfully use a prosthesis for ambulation.59

Prosthetic devices are plentiful and represent many different levels of technological advancement and sophistication. Amputees cite problems with comfort and fit as being present about 25% of the time.60 The biomechanical functions of prosthetic feet and prosthetic centers of mass have been studied, revealing important insights into the performance of these different components.61,62 Similar studies are necessary to fully explore the efficacy and advantages of newer components, particularly the microprocessor controlled knee units, for instance, the C-leg that uses variable damping and the Ossur Rheo knee that uses magnetorheological properties to change resistance.63,64 A well-fitting functional prosthesis is one of the most important factors promoting full functional restoration and vocational success.65

In a large-scale survey of members of the Amputee Coalition of America, nearly one third of the 935 respondents expressed dissatisfaction with the comfort of the prosthesis.66 Frequency of use and satisfaction with the device were significantly higher among those with the shorter timing to first prosthesis fitting even controlling for an array of respondent characteristics.66 This suggests that early fitting and prosthetic training can be important in the optimal use of prosthetic devices.

In a companion study of Amputee Coalition of America members 79.9% had phantom pain, 67.7% had limb pain, and 62.3% had back pain67 For 38.9% of respondents in this survey, the phantom pain was described as severe and bothersome. Using multivariate analysis techniques depressive symptoms were significant predictors of pain level and discomfort even controlling for other factors.67 Although cause and effect are unclear, these findings suggest that assessment for, and treatment of, depression has a role in amputee care. In this sample, 28.7% were depressed and risk factors included near poverty living, younger age,15–54 and the presence of comorbid conditions.68 For these depressed amputees, 32.9% who wanted treatment could not access the healthcare system for this problem.

Pain can unfortunately become a profound secondary problem for amputees. Most amputees (80–100%) will experience nonpainful phantom sensations.69 Many (50–75%) develop phantom pains at some point after amputation.69 Approximately one-quarter of amputees develop phantom pain that is long-lasting.70 This condition is a disabling one that does not respond well to most therapies and medications.69,71 Although many treatments have been used for this condition, none has been found to be uniformly effective, and there is little evidence from randomized controlled trials to guide treatments.70 Amputees can suffer from residual limb pain in the remaining stump. The phenomenon of phantom pain is such that it is perceived in the amputated part of the limb. The mechanisms for these painful conditions are quite different. The origin of phantom pain is thought to reside in the central nervous system, in the “neruomatrix,” as described by Melzack72 In this model, the brain is used to seeing a limb and, when amputation occurs, there is a deficit of input that results in the phantom pain. This can explain the lack of success of peripheral nerve and spinal interventions. Stump pain is quite different and can be the result of many different causes. They are divided into prosthetic socket interface issues such as poor alignment of the device or an ill-fitting prosthesis that puts excessive pressure over a specific area. The residual limb also can develop teninopathies, painful bursae, and boney spurs, which all contribute to such pain. These painful conditions should be subjected to more randomized controlled trials to examine the optimal strategies for management. Several investigations addressed the issue of preventing phantom pain with preoperative use of anesthetics and pain medications.73,74 The promise of such treatment requires more investigations.
Vocational disabilities are all to frequent, particularly for the person incurring an amputation.\textsuperscript{75,76} Upper-limb amputations caused by motor vehicle crashes or industrial accidents are declining in the United States, yet for those amputees, there are many vocation challenges. These patients are often required to change jobs or become retrained. Factors such as low educational level and prosthetic comfort are associated with less successful job reintegration, underscoring the need for comfortable prostheses and vocational interventions.\textsuperscript{65,76} Pain in the residual limb or the presence of phantom pain negatively impact vocational success, highlighting the need for optimal pain control measures for this population of amputees.\textsuperscript{65}

A retrospective cohort of persons who underwent a lower-limb trauma-related amputation was studied to examine their long-term outcomes and explore the influences of rehabilitation services.\textsuperscript{77} Patients were identified with a principal or secondary diagnosis of a trauma-related amputation to the lower extremity at the University of Maryland Shock Trauma Center between 1984 and 1994. Those with spinal cord injury or traumatic brain injury were excluded. Approximately one fourth of persons with a trauma-related amputations reported ongoing severe problems with the residual limb, including phantom pain, wounds, and sores. The number of inpatient rehabilitation nights after acute surgical care significantly improved amputees’ ability to function in their physical roles, increased their vitality, and reduced their bodily pain. Inpatient rehabilitation was also significantly correlated with improved vocational outcomes.\textsuperscript{77} These findings suggested a beneficial effect of inpatient rehabilitation in improving long-term outcomes of persons with trauma-related amputations.

Rehabilitation services today are provided at comprehensive inpatient rehabilitation units attached to acute-care hospitals or free-standing rehabilitation hospitals. Less-intense rehabilitative services also are administered in skilled nursing facilities, at outpatient rehabilitation facilities, or at home through home health care. Despite the importance of dysvascular amputations and the potential for enhancement of function through appropriate rehabilitation, it remains unclear which rehabilitation setting following amputation results in the best outcomes. This is a topic that has received little research attention.

Recent investigations demonstrated that rehabilitation services provided in a comprehensive inpatient rehabilitation unit are rare for persons undergoing lower-limb amputations. In a statewide study using Massachusetts Hospital discharge data for 1997, 33% of dysvascular amputees were sent directly home, 32% went to a SNF, and only 16% received inpatient rehabilitation following acute surgical care.\textsuperscript{78} Similarly, low utilization rates were noted in Maryland, where only 9.6% of dysvascular amputees received inpatient rehabilitation following amputation.\textsuperscript{79,80}

Postacute discharge destinations—inpatient rehabilitation, skilled nursing facility (SNF), or home—and their influences on outcomes were addressed using administrative data.\textsuperscript{78} Medicare Claims data for 1996 were used to identify a cohort of elderly persons with major lower-limb dysvascular amputations and 1-yr outcomes were derived by analyzing claims for this cohort in 1996 and 1997. There were 2468 elderly amputees. One-year mortality was 41%. Multivariate probit models controlling for patient characteristics indicated that patients discharged to inpatient rehabilitation were significantly ($P < 0.001$) more likely to have survived 12 mos after amputation (75%) than those discharged to a SNF (63%) or those sent home (51%). Acquisition of a prosthetic device was significantly ($P < 0.0001$) more frequent for persons going to inpatient rehabilitation (73%) compared with SNF (58%) and home (49%) dispositions. The number of nonamputee-related hospital admissions was significantly less for persons sent to a rehabilitation service than for those sent home or to a SNF. Subsequent amputations were significantly ($P < 0.025$) less likely for amputees receiving inpatient rehabilitation (18%) than for those sent home (25%). This investigation demonstrated that inpatient rehabilitation care immediately after acute care resulted in reduced mortality, fewer subsequent amputations, greater acquisition of prosthetic devices, and greater medical stability than for patients who were sent home or to a SNF. Such information is vital for health policy makers, physicians, and insurers. These findings suggest that inpatient rehabilitation care is effective for dysvascular amputees.

**Summary and Recommendations**

This review examined issues regarding effectiveness of care, services use, and outcomes for persons with musculoskeletal disorders. For persons who underwent elective unilateral joint replacement, appropriate care can be provided in less intense and more cost-effective settings such as nursing facilities or by using well-organized home-based care. Persons with other concurrent major disabling conditions however may need inpatient rehabilitation.

For patients with hip fractures, there is evidence that a well-structured home-based program or outpatient program in selected individuals can be successful. Inpatient rehabilitation does seem, however, to afford benefits to this often frailer population. This is particularly true when there is
cognitive impairment. More prolonged exercise regimens after the surgical wounds are healed can have modest benefits, particularly in this frail population. Critical treatment pathways and care guidelines should be developed and adopted for persons post elective total joint replacement and for those patients incurring hip fractures.

Cost-effectiveness of care has not been as thoroughly studied for persons with these conditions, particularly in the setting of reduced inpatient rehabilitation lengths of stay. Such analyses are difficult and must take into account both the direct costs as well as indirect subsequent costs such as hospital readmissions due to suboptimal medical stability. The broad field of physical medicine and rehabilitation could benefit by more health services and outcomes research initiatives.

Dysvascular amputations are on the rise in the United States with minority persons at higher risks for such limb loss. Public policy initiatives to sort out the underlying risk factors that drive these higher rates is a first step in understanding and preventing excess morbidity due to dysvascular amputations.

Pain and depression are problems that continue to affect persons who incur limb loss. Recent evidence suggests that inpatient rehabilitation after acute surgical care improves function and reduces mortality and subsequent healthcare utilization, yet seems to be underused.

Prosthetic devices are becoming increasingly more sophisticated with computer-driven knee mechanisms, many different types of prosthetic feet, and newer materials that bring considerable strength and low weight. Studies that delineate specific patient characteristics that are associated with optimal use of such devices would be of value. Comfort is also an important aspect of the device and one that is frequently problematic. Efforts to improve comfort through the use of newer materials and designs are worthwhile.

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Physiological Basis of Fatigue

ABSTRACT


This work summarizes our knowledge of the physiological basis of fatigue and the effects of exercise and pharmacological interventions on fatigue. Fatigue may be defined as physical and/or mental weariness resulting from exertion, that is, an inability to continue exercise at the same intensity with a resultant deterioration in performance. The concept of deconditioning in patients is discussed as well as the implications for their rehabilitation and exercise. Because fatigue may result from a number of causes, including loss of muscle mass, deconditioning, nutritional deficiencies, oxygen delivery, and anemia, it should be treated comprehensively. Antifatigue therapy should be the standard of care for most chronic conditions associated with fatigue.

Key Words: Fatigue, Exercise, Physiology, Pharmacology, Rehabilitation

A broad array of clinical conditions is associated with extreme levels of fatigue. Chronic renal failure, congestive heart failure, cancer, musculoskeletal diseases, chronic fatigue syndrome, chronic obstructive pulmonary disease, human immunodeficiency syndrome/acquired immunodeficiency syndrome, (HIV/AIDs) and more are associated with mild-to-often debilitating fatigue. Aging is also associated with fatigue, which may lead to frailty and disability. Perhaps the chronic condition most associated the fatigue is cancer. Cancer and its treatment are associated with a broad range of physiological and metabolic adaptations, including cachexia, muscle wasting, anemia, and inflammation. One of the most commonly reported symptoms of cancer is a reported lack of energy or fatigue. Fatigue is highly prevalent (between 80 and 99%) among cancer patients who undergo treatment with chemotherapy, radiotherapy, or both.

A patient’s perception of fatigue results from many factors related to physiological, psychological, or cognitive changes. Fatigue also may result from a lack of sleep. The purpose of this review is to describe the physiological basis of fatigue and how these factors may be related to fatigue related to chronic disease or its treatment. There is a large body of literature on fatigue associated with cancer and its treatment. However, few studies have examined the physiological or biological basis of this fatigue. It is very likely that many aspects of cancer-related fatigue are quite different from fatigue related to physical exertion. However, it is also likely that the underlying causes of fatigue related to exertion share common mechanisms with fatigue related to chronic illness. A
Among the conclusions of this conference were the following:

1. Too many cancer patients with pain, depression, and fatigue receive inadequate treatment for their symptoms.
2. Clinicians should use brief assessment tools routinely to ask patients about pain, depression, and fatigue and to initiate evidence-based treatments.
3. Research is needed on the definition, occurrence, assessment, and treatment of pain, depression, and fatigue alone and together through adequately funded prospective studies.

For the purpose of this review, we will define fatigue as physical and/or mental weariness resulting from exertion, that is, an inability to continue exercise at the same intensity with a resultant deterioration in performance. The term “fatigue” appears often in the medical literature but rarely is an operational definition included. Fatigue associated with cancer also may include tiredness or lack of sleep. However, we will use the term “fatigue” as it relates to exertion (such as walking, climbing stairs, or participating in normal activities of daily living).

Because activities of daily living require muscular effort and increased levels of physical activity, an understanding of the causes of fatigue during exertion is helpful in describing the causes of the fatigue associated with other diseases (including cancer), aging, or severe deconditioning (from immobilization or prolonged bed rest). Fatigue resulting from increased physical activity may result from a number of metabolic adjustments to increased muscular activity. Physical activity varies with respect to intensity and duration for any individual. It is important to note that physical conditioning of an individual determines the type of exertion and its intensity. For example, walking at a pace of 2–3 miles per hour would be considered a low-intensity aerobic exercise for a healthy, normally active young man or woman, whereas the same walking pace would be considered high intensity, anaerobic exercise for a severely deconditioned patient with heart failure.

**Aerobic Capacity**

Physical function may be measured in a great many ways; however, one of the most fundamental measures is maximal aerobic capacity or VO2max. VO2max (volume of oxygen consumed during maximal aerobic exercise or the maximal rate of oxygen consumption) is defined by the Fick equation (\( VO_2 = \text{cardiac output} \cdot \text{arteriovenous oxygen difference} \)). VO2max is expressed as either milliliters of \( O_2 \) consumed \( \cdot \text{kg}^{-1} \cdot \text{body weight} \cdot \text{min}^{-1} \) or liters of \( O_2 \) consumed \( \cdot \text{min}^{-1} \). VO2max is a total integrated measurement that is determined by the following: the capacity to inhale sufficient quantities of oxygen, extract oxygen by the lung, carry oxygen by the red blood cells, deliver oxygen (blood) by cardiac output, diffuse oxygen through capillaries, diffusion into muscle cells and binding to myoglobin, and oxidative phosphorylation in muscle mitochondria for ATP production. This equation demonstrates that there are two important determiners of VO2max, central factors that control the delivery of oxygen to skeletal muscle and the capacity of skeletal muscle to extract and use oxygen for ATP during exercise. Regularly performed aerobic exercise increases VO2max through a number of mechanisms: (1) increased cardiac output resulting from a plasma volume expansion (approximately 15%) and increased stroke volume as a result of cardiac hypertrophy and (2) improved capacity to extract and use oxygen by skeletal muscle. This enhanced oxidative capacity of muscle is caused by increased capillarization, mitochondrial density, and myoglobin content.

Few individuals actually exercise or work at an intensity that is equal to their VO2max during the normal course of a day. However, a diminished maximal aerobic capacity can greatly limit the performance of activities of daily living. For example, the oxygen cost of walking at a pace of 2 miles per hour (a relatively slow pace) for a 60-kg individual is almost 0.8 liters of oxygen per minute. If an individual has a VO2max of 15 ml/kg per minute, he or she can only consume a maximum of 0.9 liter of oxygen per minute. For people who are functionally intact with no impairment in oxygen delivery or use, virtually all activities of daily living are performed at a low to moderate exercise intensity. Most individuals pace themselves as an intensity of about 50% of VO2max when asked to perform work over a sustained period of time (walking, for example). For men and women with very low levels of VO2max, one can see that self-paced activities at 50–60% of maximal capacity is significantly lower than the oxygen costs of most activities of daily living.

**Anemia and Aerobic Capacity**

Under most conditions, the delivery of oxygen (cardiac output) limits VO2max. That is, the capacity to extract and use oxygen by skeletal muscle is greater than the capacity to deliver oxygen. Because of this, a number of investigators have demonstrated a remarkably close relationship between hemoglobin and VO2max. Increasing blood hemoglobin concentration (from anemic to normal or
from normal to supernormal) has been demonstrated to increase VO$_{2\text{max}}$ and submaximal exercise performance. Anemia caused by malnutrition has been demonstrated to limit functional status and work capacity. On the other hand, aero-
bic exercise performance in athletes can be sub-
stantially improved by increasing hemoglobin lev-
els above normal through the use of recombinant human erythropoietin.10

Muscular activity may be generally classified as anaerobic or aerobic. Aerobic activities are per-
fomed at intensities that require oxygen consump-
tion lower than an individual's VO$_{2\text{max}}$ whereas anaerobic activities are performed at intensities that are greater than VO$_{2\text{max}}$. Exercise intensities above VO$_{2\text{max}}$ must rely on a combination of aero-
bic and anaerobic metabolism and will result in fatigue when sustained over an extended period of time.

**Types of Exertion and Causes of Fatigue**

**Submaximal Activities**

During exercise of any intensity, skeletal mus-

cle produces and consumes lactic acid as a fuel for energy production. During low-intensity exercise, the use of lactic acid as a fuel prevents its accumula-
tion. However, as exercise intensity (and oxygen consumption) increases, the production of lactic acid increases and, at some intensity, production becomes greater than oxidation and intracellular lactic acid accumulation occurs. The exercise in-
tensity at which lactic acid accumulation occurs has been referred to as the anaerobic threshold or the lactate threshold. This increasing blood (and muscle) lactic acid level results in muscle fatigue as well as an increased respiration and heart rate, and an overall feeling of fatigue. The ex-
ercise intensity that generally corresponds to the anaerobic threshold in sedentary individuals is ap-
proximately 60% of VO$_{2\text{max}}$. This means that for a cancer patient with an already low VO$_{2\text{max}}$, per-
foming most activities of daily living requires an intensity that is greater than the anaerobic thresh-
old. Therefore, it is easy to see why most physical activity performed by this person will lead to an overwhelming feeling of fatigue.

**Glycogen Depletion**

A number of early studies demonstrated that depletion of skeletal muscle glycogen stores coincided with fatigue during submaximal exercise. Bergstrom et al.13 reported that a high-
carbohydrate diet prolonged time to exhaustion by 220% compared with a high-protein, high-fat diet and by 50% when compared with a mixed diet. They showed that consumption of a high-carbohy-
drate diet resulted in the highest muscle glycogen concentration compared with a mixed diet and a high-protein, high-fat diet. These results have been confirmed by a number of studies; however, the mechanism for this effect is not clear. That is, despite an abundant source of fuel in the form of fatty acids, the depletion of muscle glycogen re-
sults in fatigue. Glycogen provides a carbon source for the tricarboxylic acid cycle (TCA) provides NADH, FADH$_2$, which then is converted into ATP by the electron transport system. ATP and GTP are also directly produced by the TCA cycle. Thus, the glycogen ultimately leads to increased ATP production both anaerobically (glycogenolysis) and through the TCA cycle (aerobic metabolism), and thus results in improved performance. However, Baldwin et al.16 recently reported that glycogen availability had no effect on maintaining the concentra-
tion of TCA cycle intermediates or the total adenosine nucleotide pool (ATP + ADP + AMP), suggesting that the mechanism for the improve-
ment in performance with high muscle glycogen levels may not be as simple as previously believed. A study in situ in rodents suggests that a decrease in sarcoplasmic reticulum glycogen and sarcoplas-

cmic reticulum glycogen phosphorylase occurring with a reduction in whole muscle glycogen and tetanic force resulted in a significant reduction in sarcoplasmic reticulum Ca$^{2+}$ uptake. Thus, this is a potential mechanism for the fatigue that oc-
curs with a reduction in intramuscular glycogen concentrations. This possibility awaits further sci-
cientific inquiry.

**Dehydration**

Dehydration will impair physical performance. As little as a 2% reduction in body weight will impair endurance exercise performance. Further, Montain et al.19 reported that a 4% reduction in body weight is adequate to reduce short-term (exhaus-
tion reached in approximately 4 mins) exercise capacity. However the mechanism(s) for this re-
duced performance, which includes impaired met-
abolism and/or hyperthermia, has not been ade-
quately answered until recently. Gonzalez-Alonso et al.20 examined the effect of the reduced blood flow associated with dehydration on substrate de-

delivery, metabolite, and heat removal to and from the active skeletal muscles as well as fuel utiliza-
tion across the leg. These investigators concluded that fatigue was the result of hyperthermia and not the result of altered muscle metabolism.

**Nutritional Deficiencies**

Loss of appetite often is associated with chronic diseases and/or aging. Decreased food in-
take can result in involuntary weight loss and spec-
cific nutritional deficiencies. Vitamin D deficiency
is associated with muscle weakness, type II fiber atrophy, and accelerated sarcopenia. \(^{21,22}\) Bischoff et al. \(^{23}\) found that among elderly women in a long-term care facility, vitamin D deficiency is associated with an increased rate of falling and that a single intervention with vitamin D reduced the risk of falling by 49% compared with a calcium only-supplemented group. They concluded that the “impact of vitamin D on falls might be explained by the observed improvement in musculoskeletal function.” In an older (>65 yrs) population of community-dwelling men and women, vitamin D supplementation (single intramuscular injection of 600,000 IU 25OHD) improved functional capacity but did not have any effect on rate of falls. These and other studies demonstrate a strong effect of vitamin D on muscle function. \(^{24}\) Treatment for weakness or fatigue that may be associated with chronic disease, particularly in elderly people, should include assessment of vitamin D status or the use of a vitamin D supplement.

Protein energy malnutrition (PEM) impairs muscle function. \(^{25}\) PEM results in a decrease in high energy phosphate levels in skeletal muscle \(^{26}\) as well as a number of components of contractile function. \(^{27}\) Refeeding elderly, malnourished patients (15 g of protein and 836 kJ, twice daily) increased muscle strength and function compared with a well-nourished age-matched control group strongly indicating that intracellular energy metabolism is affected by PEM refeeding can have a rapid and powerful effect on muscle function, functional capacity, and the feeling of fatigue. In addition, long-term PEM will greatly reduce muscle size, ultimately diminishing strength.

**Central Fatigue**

Central fatigue is impaired muscular performance that arises from the central nervous system. There are two general ways to study central fatigue. The first way and likely the best way is by using a technique where “added force” is determined. This occurs by superimposing a supramaximal electrical stimulus of a muscle onto a maximal voluntary contraction for that muscle. Any “added force” generated in addition to that produced by the maximal voluntary contraction is indicative of an impairment from the central nervous system down to the level proximal to the neuromuscular junction. Thus, this is a fairly direct way to determine central fatigue. This can be done after exercise and/or after an intervention thought to induce central fatigue. A second way is to exogenously provide a substance thought to induce central fatigue and look at its effect on exercise capacity. However, this is indirect because you do not know if the substance had peripheral and/or central effects. Further, this technique is usually undertaken in animal models.

Recent data suggest that prolonged exercise in a thermoneutral \(^{28–32}\) or hot \(^{33}\) environment and exhaustive shorter-term exercise (30–45 mins) results in a significant level of central activation failure or central fatigue. Lepers et al. \(^{28,29}\) reported that 2–5 hrs of cycling at 55% of \(\text{VO}_{2\max}\) resulted in an 8% reduction in the ability to activate the quadriceps in trained endurance athletes. Further, Millet et al. \(^{31}\) reported that maximal voluntary activation was reduced by 30.2% in the knee extensors and by 27.7% in the plantar flexors after an ultra-marathon. Nybo \(^{34}\) reported that 3 hrs of cycling at 60% of \(\text{VO}_{2\max}\) resulted in a significant reduction in muscle activation in trained endurance athletes when placebo was ingested but not when glucose was ingested suggesting that central fatigue can be induced by exercise induced hypoglycemia. Nybo and Nielsen \(^{33}\) reported that central activation was 34% lower in individuals who exercised for 50 mins at 60% of \(\text{VO}_{2\max}\) in a hot (40°C) environment than in those same individuals exercising for 60 mins in a thermoneutral (18°C) environment. The subjects in that study were trained endurance cyclists. Bentley et al. \(^{35}\) reported that 30 mins of exercise at 80% of \(\text{VO}_{2\max}\) followed by 4 × 60 secs at 120% of \(\text{VO}_{2\max}\) in trained cyclists led to an approximately 6% deficit in muscle activation.

**Effects of Aerobic Exercise on Brain Dopamine**

Drugs such as methylphenidate and pemoline act to increase brain dopamine concentrations and reduce fatigue in individuals with cancer. Other interventions that have been shown to beneficially alter dopamine metabolism in the brain are an acute bout of aerobic exercise and chronic aerobic exercise training. Gilliam et al. \(^{36}\) reported that chronic exercise training (1 hr/day, 6 days/wk for 12 wks) increased the number of dopamine receptors in the striatum of rats by 48%. Meeusen et al. \(^{37}\) reported that 60 mins of acute exercise significantly increased the dopamine concentration of the striatum during exercise and for 2 hrs after exercise. Heyes et al. \(^{38}\) reported that exhaustive running in rats increased dopamine concentrations in the striatum significantly by 10%. Hattori et al. \(^{39}\) reported that extracellular dopamine in the striatum of rats was increased by approximately 25% as a result of treadmill running for only 20 mins. Wilson and Marsden \(^{40}\) reported a approximately 80% increase in dopamine in the extracellular fluid of the nucleus accumbens in response to 20 mins of treadmill exercise in rats. In contrast, in the only human study examining the effects of exercise on striatal dopamine release. Wang et al. \(^{41}\) found no significant effect of intense aerobic exercise. One possible explanation for this negative result is methodological. The dopamine concentration only
increases 80% in response to exercise in rats but administration of methylphenidate can increase dopamine by approximately 600%. Thus, the increase in brain dopamine concentration in humans (it has been shown to be an 80% increase in rats using the microdialysis approach) may not be a large enough to be detectable by using the positron emission tomography scan. In an open labeled pilot study using 10–30 mg/day of methylphenidate in advanced cancer, Sarhill et al. reported that 9 of 11 patients had reduced fatigue after 7 days of treatment. The most prominent side effect of this therapy was insomnia in 5 of the 11 patients.

**Short-Term High-Intensity Exercise**

During very short-term, high intensity exercise (5–10 secs), maximal power output declines and correlates well with the decline in phosphocreatine (PCr). At the same time, the [H+] concentration is decreasing, likely as the result of the consumption of protons when PCr + ADP + H+ gets converted to Cr + ATP. Early in vitro investigations at temperatures much lower than physiology suggested the [H+] is a major contributor to fatigue; however, more recent investigations suggest that at or near physiological temperature the [H+] has little effect on the contractile processes. Additionally, in some instances, force recovers more rapidly than pH during recovery from fatiguing contractions. There seems to be a large amount of data suggesting that an increase in the Pi concentration is a major contributor to fatigue during intense contractions. Furthermore, factors affecting strength that are considered neurological in origin are motor unit recruitment, motor unit firing rates, and antagonist muscle co-contraction. It is clear that in some disease states such as multiple sclerosis and chronic fatigue syndrome, there is a reduction in the ability of muscle activation (motor unit recruitment and/or motor unit firing rates), which leads to a reduction in muscle strength.

**Factors Limiting Strength**

Factors that limit the strength of muscle force generation can be broadly classified into factors that deal with the muscle itself and factors within the nervous system. Generally speaking the more muscle mass an individual has the greater the ability to produce force. However, type II (fast twitch) muscle fibers exert more force than type I muscle fibers thus the fiber type composition and size of type II and type I fibers also play a major role. With regard to the nervous system and muscle force generation many factors are involved. First, an inability to recruit all available motor units (motor neuron and all of the muscle fibers it innervates) may limit performance. Second, motor unit firing rates may be sub optimal. The faster the motor unit firing rates the greater the muscle force that can be generated. For movements involving more than one muscle group the ability to synchronize the activation of motor units from different muscle groups is of paramount importance. Coactivation of antagonist muscle groups can also limit muscle force generating capacity of agonists. Resistance training acts to reduce the coactivation of antagonists. Further, inhibition of force generation resulting from activation of the Golgi tendon organ, referred to as neural inhibition, can also limit force generating capacity and resistance training seems to reduce this neural inhibition.

Cross-sectional area may be the most important determinant of strength (maximal force production). Akima et al. reported a correlation of 0.827 between muscle cross-sectional area and maximum knee extensor torque in men and a correlation of 0.657 in women. In that study, 164 individuals were studied and were grouped into five age groups spanning from ages 20 to 84. However, in a group of frail elderly subjects, muscle cross sectional area explained approximately 6% (after controlling for gender, r² = 0.06, P < 0.05) of the variability in muscle strength. Loss of muscle mass with advancing age (sarcopenia) is associated with age-associated loss of strength; however, it may not be the most important variable among extremely inactive people. As mentioned previously, factors affecting strength that are considered neurological in origin are motor unit recruitment, motor unit firing rates, and antagonist muscle co-contraction. It is clear that in some disease states such as multiple sclerosis and chronic fatigue syndrome, there is a reduction in the ability of muscle activation (motor unit recruitment and/or motor unit firing rates), which leads to a reduction in muscle strength.

**Fatigue in Chronic Conditions**

**Multiple Sclerosis**

Increased fatigability and reduced muscle strength are observed in individuals with multiple sclerosis when compared with control subjects. Reduced muscle oxidative capacity results in increased fatigability when muscles are electrically stimulated but during voluntary contractions it seems that fatigue is a result of impaired muscle activation possibly at the level of excitation–contraction coupling. At least part of the reduced force generating capacity in individuals with multiple sclerosis may be attributable to the inability to activate the muscle mass that they have. However, another major factor resulting in reduced muscle strength is reduced muscle fiber size. Muscle fiber
size is 26% smaller in individuals with multiple sclerosis compared with control subjects.55

### Chronic Heart Failure

Increased skeletal muscle fatigability is evident in chronic heart failure (CHF),57 which may at least in part the result of reduced muscle blood flow to the working muscle and is definitely attributable to metabolic abnormalities intrinsic to skeletal muscle.57–61 The changes in skeletal muscle that result in increased fatigability are most likely related to reduced muscle oxidative capacity62,63 in addition to reduced type I muscle fibers and increased type II B muscle fibers.63 These changes may be the result of disuse and/or the direct effects of the disease.

CHF also results in reduced muscle mass and muscle strength,64 in this patient population. Muscle cross-sectional area significantly correlates with peak VO2, suggesting that, in patients with CHF and in the elderly,65 muscle mass is a significant predictor of peak aerobic capacity. Elevated levels of the proinflammatory cytokines interleukin-6 and tumor necrosis factor alpha have been reported in individuals with CHF, and high levels of these cytokines have been implicated in muscle wasting in elderly individuals.66 Hambrecht et al.67 reported that individuals with CHF have reduced muscle insulin-like growth factor-I mRNA and protein and that this is significantly correlated with muscle cross-sectional area. Resistance upregulates muscle IGF-I mRNA and protein,68,69 resulting in muscle hypertrophy.

van den Berg-Emons et al.70 examined the effects of aerobic exercise training on levels of physical activity and quality of life. They found that although the exercise training increased aerobic power (17%), 6-min walk distance (10%), and strength (13–15%), no changes in physical activity or quality of life were seen compared with a control group of patients receiving standard therapy but no exercise. On the other hand, in a similar group of patients with CHF,71 exercise training decreased perceived dyspnea during submaximal exercise and improved Minnesota Living with Heart Failure Score. Six-minute walk time was improved by 65% with exercise training (compared with activity restriction) in patients with severe chronic heart failure (ejection fraction 21 ± 1%). Although the number of well-controlled, randomized trials examining the effects of exercise in people with chronic heart failure is few, they have all demonstrated positive results. Differences in improvements in functional capacity may be the result of inherent differences in baseline functional status, severity of disease, and the intensity, frequency, and duration of the exercise intervention.

### Chronic Renal Failure

This condition leads to a reduction in hemoglobin concentration,72 a decrease in muscle mass,73 and a reduction in muscle quality termed “uremic myopathy.”74 All of these manifestations can lead to increased fatigability. Correction of the reduced hemoglobin concentration via the administration of recombinant erythropoietin does not improve maximal oxygen consumption proportionally. Marrades et al.75 reported that erythropoietin therapy resulted in increased hemoglobin 69% and a 33% increase in maximal oxygen uptake. The impaired O2 extraction is the result of reduced O2 conductance from the muscle capillary to the mitochondria.74,75,77 Impaired oxidative metabolism intrinsic to the muscle does not seem to be a source of fatigability in chronic renal failure.74,76 The major factor that seems to contribute to the reduced O2 conductance from muscle capillary to mitochondria in chronic renal failure is a low number of capillaries per muscle fiber.78,79

The reduction in muscle strength in individuals receiving hemodialysis is the result of a reduction in muscle contractile tissue and not the result of an inability to activate the available muscle.73 In addition, muscle quality as measured by force generating capacity per unit contractile tissue was not reduced in individuals on hemodialysis.73 The reduction of muscle mass in chronic renal failure seems to be attributable to increased protein degradation80 and reduced protein synthesis.81 The increased muscle protein degradation is the result of activation of the ATP-dependent ubiquitin–proteasome pathway which is further activated by acidosis present in uncontrolled chronic renal failure.80

Although anabolic steroids have been used frequently for the treatment of anemia associated with chronic renal failure, their effects on body composition and function have not been determined in this population. The potential for anabolic steroids/testosterone to be beneficial is likely given the fact that these patients suffer from malnutrition, reduced muscle mass, and fatigue.82 Johansen et al.82 reported that in patients undergoing dialysis for at least 3 mos, 100 mg of nandrolone decanoate given weekly for 6 mos increased lean body mass by 4.5 kg and time to complete a walking/stair climbing test improved significantly by 11.5% whereas it became slower by 8.8% in the control group. Those receiving nandrolone also reported less fatigue than control patients after the intervention period. Thus, anabolic therapies would seem to be beneficial in this population of patients. This patient population also should be a target for active exercise and rehabilitation therapies. The reduced muscle capillary density, decreased muscle protein synthesis, and fa-
tigue are likely to be strongly influenced by increased levels of physical activity.

In patients with end-stage renal disease on hemodialysis, 6 mos of aerobic exercise training resulted in substantial increases peak VO₂, and exercise time to exhaustion. The exercise training was more effective in subjects performing their exercise on nondialysis days compared with those exercising on the days that they received dialysis.

Chronic Fatigue Syndrome

The causes of fatigue in this disease seem to be proximal to impaired muscle metabolism. In addition, there seems to be minor morphological abnormalities of skeletal muscle in this disease. Byrne and Trounce reported that carnitine, glycocytic enzymes, and mitochondrial enzymes were normal in individuals with chronic fatigue and those with fibromyalgia syndrome, suggesting that impaired muscle metabolism is not the reason for the increased fatigability of these conditions. Kent-Braun et al. reported greatly reduced central activation of muscle during sustained contraction in individuals with chronic fatigue syndrome (CFS), implicating central factors in fatigue during exercise. McCully and Natelson examined oxygen delivery to skeletal muscle in CFS using continuous-wavelength near-infrared spectroscopy and found that the time constant for oxygen delivery was 36.8% longer in individuals with the disease than control subjects. However, in a subsequent study the same investigators observed that blood flow was not impaired in patients with CFS relative to controls. A frequent finding in CFS is impaired recovery of force generating capacity after fatiguing exercise. Indeed, Paul et al. reported that force-generating capacity was impaired in CFS patients for as long as 24 hrs after fatiguing isometric contractions but not in controls. There is a fair amount of evidence suggesting that there is physical and cardiovascular deconditioning in CFS, which may be reversible with exercise training. However, muscle wasting or atrophy does not seem to be a universal or major problem in CFS as Lane et al. reported that muscle fiber atrophy was only present in 10.4% of the cases of CFS.

Aging

Normal aging is associated with a decline in muscle strength and mass and a reduction in VO₂max. After the age of 30, the decline in VO₂max seems to be about 10% per decade, whereas the loss in muscle strength is approximately 12–14% per decade. This decrease in maximal aerobic capacity results from sarcopenia, reduced maximal heart rate, and reduced overall levels of physical activity. Fleg and Lakata demonstrated that muscle mass accounts for most of the variability in VO₂max among people older than the age of 60 yrs. The decrease in strength means that a given load (e.g., carrying a bag of groceries) is a greater percentage of maximal force production. The greater the percentage of maximal force production, the fewer number of repetitions possible and the slower the speed of contraction. Thus, the decline in strength ultimately leads to greater fatigue or shorter endurance or both. Further, the age-associated decrease in maximal aerobic capacity results in a greater relative intensity at any given submaximal energy expenditure. The greater the relative intensity (%VO₂max), the shorter the exercise duration that is possible because of fatigue. It is clear that maximal force generating capacity decreases with age. What is less clear is the relationship between fatigue or endurance at a given percentage of maximal force generating capacity and age. Studies report that fatigue is less similar, or greater for older individuals than young individuals at a given percentage of maximal force generating capacity. Of interest from a practical standpoint is that older women classified as fallers (unexplained contact with the ground during the previous 18 mos) had reduced endurance time during isokinetic knee extensions and prolonged recovery time after the knee extensions than older women who were not classified as fallers and than younger women indicating that muscle endurance may be related increased risk of falls in elderly women.

Testosterone and Sarcopenia

Morley et al. studied 37 men ages 69–89 yrs old, 26 of whom had a mean total testosterone level of less than 272 ng/dl. They were administered 200 mg of testosterone enanthate every 2 wks for 3 mos. They reported a ninefold increase in bioavailable testosterone and significant increase in right hand muscle strength. Sih et al. reported that 12 mos of testosterone replacement (biweekly injections of 200 mg) in hypogonadal elderly men resulted in a significant increase in bilateral grip strength. Bhasin et al. examined the effects of 10 wks of testosterone replacement (100 mg/vk) on body composition and strength in seven hypogonadal men ages 19–47. By day 15, serum testosterone had increased from 7.9 to 509 ng/ml. There was an 8.8% increase in fat-free mass, an 11% increase in triceps cross-sectional area, and a 7% increase in thigh cross-sectional area. This group has also demonstrated that both older and young subjects demonstrate similar responses to testosterone injections. Strength on the bench press increased by 22% and on the squat exercise increased by 45%. Urban et al. administered 100 mg of testosterone enanthate week to six elderly men (mean age 67) for 4 wks and observed significant increases in muscle strength of the ham-
strings and quadriceps. These investigators also observed that the fractional synthetic rate of muscle protein was increased by 200% as a result of testosterone administration. Brodsky et al. administered 3 mg/kg of testosterone biweekly to hypogonadal men (no age given) for 6 mos and reported a 15% increase in fat-free mass and a 56% increase in the muscle fractional protein synthetic rate. Snyder et al. reported that administration of a testosterone patch to men older than 65 yrs of age for 9 mos, resulted in a significant 1.9 kg increase in lean mass. However, it did not improve the strength of leg extension or flexion. Schroeder et al. reported that oxandrolone administration (20 mg/day) for 12 wks to elderly men mean age 72 resulted in a 6.3% improvement in the leg press and a 6.3% improvement for the leg flexion. Recently, Steidle et al. reported that the application 100 mg/day of a testosterone gel over the course of 90 days resulted in an improvement in lean body mass of 1.7 kg and a reduction in body fat of 1.2%. Thus, all but one of the studies cited found increases in strength with testosterone administration and all of the studies that examined the effects of testosterone on body composition found an increase in fat-free mass and/or muscle mass.

Megestrol acetate (MA) is a powerful appetite stimulant that is commonly used to treat involuntary weight loss in elderly people, patients with HIV-associated wasting, and cancer. MA is a synthetic progestin and its use is associated with suppressed testosterone and ACTH secretion. Lambert and coworkers examined the combined effects of MA (800 mg/day), testosterone replacement (weekly injections of 100 mg), and progressive resistance exercise training (80% one-repetition maximum (1RM), three sets of eight repetitions, 3 days/wk) in a group of underweight elderly men (n = 30, 67.0 ± 5.8 yrs) during a 12-wk period. The administration of MA resulted in an average 3.8-kg weight gain in all subjects with a decrease in muscle mass that was not affected by testosterone. Men receiving MA + exercise showed no loss in muscle and MA + testosterone + exercise resulted in an increase in both body weight and muscle size. Recently, Sullivan et al. examined the combined interaction of testosterone administration and strength training (low or high intensity, 20 or 80% of 1RM, respectively) in extremely frail, hypogonadal, old men (78.2 ± 6.4 yrs), all of whom were inpatient recuperative care patients. They saw no significant interaction between exercise and testosterone for body composition, strength, or functional capacity. High-intensity exercise produced a greater gain in strength and testosterone administration produced a greater increase in muscle size than did exercise alone.

Potential Side Effects of Testosterone Replacement in Older Hypogonadal Men

Sih et al. reported that 4 of 17 older hypogonadal men withdrew as a result of an abnormal elevation in hematocrit (>52%) during a 12-mo study where 200 mg of testosterone was administered biweekly. Hajjar et al. retrospectively assessed 45 elderly hypogonadal men receiving testosterone replacement. The treatment dose was 200 mg of testosterone enanthate or cypionate every 2 wks. They reported that 24% of the testosterone-treated subjects developed polycythemia sufficient enough to require phlebotomy or temporary withholding of testosterone injections. In one third of the individuals in whom this problem occurred it occurred less than 1 yr into treatment.

Some studies support the notion that hypogonadism may negatively alter blood lipids and that testosterone replacement may improve blood lipids in these individuals. However, the administration of testosterone to individuals who already have “normal” testosterone concentrations may have adverse effects on blood lipids. Thus, the effect of testosterone replacement on blood lipids in hypogonadal men requires close scrutiny. Berg et al. reported that the restoration of normal testosterone levels in hypogonadal men did not adversely effect the total cholesterol/high-density lipoprotein or the low-density lipoprotein cholesterol/apoprotein B ratios, both of which are reflective of atherogenesis. Whitsel et al. performed a meta-analysis on the effects of testosterone on plasma lipids in hypogonadal men. They reported that the administration of testosterone esters to hypogonadal men results in a small, dosage-dependent decrease in high-density lipoprotein cholesterol but also resulted in concomitant declines in total cholesterol and low-density lipoprotein cholesterol. Thus, it seems from their conclusions that testosterone replacement may have little effect on atherogenesis as reflected by the changes in blood lipids.

As summarized by Morales et al. it seems that in placebo-controlled studies of hypogonadal men receiving androgen replacement that there is not a significant effect of such replacement on prostate specific antigen or prostate volume when compared with the placebo group. As discussed by these authors, there is controversy regarding the relationship between serum testosterone concentrations and the prostate gland. It seems firmly established that testosterone promotes the growth of an established adenocarcinoma, but it is unknown whether testosterone promotes the new development of prostate cancer. A recent meta-analysis of placebo-controlled interventions using testosterone in elderly men described the incidence of adverse events. These authors examined 19 stud-
ies of 651 men treated with testosterone and 433 with placebo. They found that rates of prostate cancer, prostate-specific antibody >4 ng/ml, and prostate biopsies were numerically high, but no statistical differences in any of these event between groups. Increase in hematocrit was the most frequent adverse event with testosterone treatment. Although, testosterone replacement therapy seems to be beneficial with regard to the restoration of muscle mass and strength, there remain questions concerning its safety that must be resolved before widespread use of androgens in the hypogonadal elderly.

Exercise

A large number of exercise trials have demonstrated that both aerobic exercise and progressive resistance exercise training results in significant and, often, quite substantial improvements even in very old and frail subjects. Meredith et al.121 demonstrated that when the frequency (3 days/wk), intensity (70% VO2max), and duration (50 min/day) were controlled aerobic exercise results in the same absolute gains in VO2max in older (60–70 yrs) as young men and women (20–30 yrs). In addition, in older people aerobic exercise increases insulin sensitivity, improves tolerance to heat, slows the loss of bone, and increases life expectancy. Progressive resistance exercise training results in a large number of positive adaptations in elderly people. Frontera et al.122 showed that high-intensity progressive resistance exercise program of the knee extensors and flexors (80% of IRM, 3 days/wk, for 12 wks) resulted in a 2- to 3-fold increase in strength, almost 15% increase in muscle size, and a concomitant increase in leg, but not arm, VO2max 123 in a group of older, previously sedentary men. Progressive resistance exercise training enhances nitrogen retention,124 bone health,125 balance,126 increased energy requirements,127,129 and levels of physical activity125 in elderly people. Fiatarone et al.50,129 have demonstrated that extremely old and frail nursing home residents show similar, substantial increases in strength. Along with increased strength, improved functional capacity and spontaneous physical activity was demonstrated. The overwhelming consensus130 is that regularly performed exercise training is both safe and effective at any age. Because a regular exercise program has an effect on the two most important causes of fatigue in older people (sarcopenia, deconditioning), an exercise prescription should be the standard of care for all elderly people.131

HIV/AIDS

Fatigue is a common problem in individuals with HIV/AIDS. In additional, muscle wasting is a prominent feature of this disease state. As described previously, a reduction in muscle mass will increase the percentage of maximal voluntary contraction that an individual has to exert for a given standard load (e.g., bag of groceries). Thus, fatigue and/or endurance time will be earlier as a result. Grinspoon et al.132 reported that the 6-min walk time (maximal distance walked in 6 mins) was best predicted by lower body muscle cross-sectional area. Anemia is an additional factor contributing to fatigue in individuals with HIV/AIDS.133 Patient reported fatigue is far more common133 in HIV-positive patients with anemia.

A number of studies have been conducted examining the effects of testosterone and anabolic steroid administration in individuals with HIV and AIDS. AIDS wasting syndrome is characterized by a 30–50% decline in circulating testosterone.134 Therefore, the administration of androgen would seem to be particularly efficacious in this population. A substantial majority of studies published on androgen administration in HIV/AIDS have a significant effect on accrual of fat-free mass. A few studies have examined muscle mass135,136 and have reported positive results. The typical dosage of testosterone is 100 mg/wk. Nandrolone decanoate and oxandrolone have been the anabolic steroids used, and the dosage range for nandrolone decanoate was fairly large (100–600 mg); however, the fat-free mass gains were similar (3.5–3.9 kg) when 100 or 600 mg were administered. A large increase in lean body mass (6.9 kg) and greatly increased nitrogen retention was observed when 20 mg/day of oxandrolone was combined with progressive resistance training.137 The combination of progressive resistance training with androgen administration may138 or may not132,135 be more beneficial with regard to increases in lean body mass than the administration of androgen alone. In the positive study of Satlter et al. a high dose of androgen (600 mg/wk of nandrolone decanoate) was administered whereas in the negative studies testosterone was administered at 100 mg/wk,135 and 200 mg/wk. Testosterone at a rate of 100 mg/wk is considered a replacement dose and, thus, the differences in dosages may be the reason for the divergent results. The combination of androgen and resistance training seems to be more efficacious than resistance training alone.133,136,137

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is the presence of an airflow obstruction attributable to either chronic bronchitis or emphysema. Chronic bronchitis occurs when an individual has a chronic cough and sputum production. Emphysema is characterized by abnormal permanent enlargement of the respiratory bronchioles and the alveoli; the airspaces distal to the terminal bron-
Choiholes. This is accompanied by destruction of lung parenchyma without obvious fibrosis. Patients with COPD have a problem with respiratory mechanics and fatigue of the diaphragm and/or intercostal muscles that may cause them to stop exercising before the exercising limb reaches functional limits. These individuals have reductions in oxidative enzyme activity, conversions to a faster fiber type within muscle, and reduced muscle capillarity. Mador et al. reported that most individuals with moderate to severe COPD do not develop contractile fatigue of the diaphragm after intense exercise to the limits of tolerance. Mador et al. reported that quadriiceps maximum voluntary contraction force was reduced by 16% when comparing healthy older adults to individuals with moderate COPD and by 24% when comparing the healthy older individuals to the individuals with severe COPD. Further, it seems that the decrement in muscle strength is greater for the lower limbs than the upper limbs. Differences in muscle strength were proportional to the reduction in thigh cross-sectional area, suggesting quantity is a greater determinant than quality. This group also examined the effects of combining strength and aerobic exercise (compared with aerobic exercise alone) on quality of life, 6-min walk distance, endurance time, and strength. They found that although the combined effects of strengthening exercises and aerobic exercise produced substantial gains in muscle strength, both modes of exercise training produced similar increases in quality of life and exercise tolerance. In other words, the increased strength seen with both forms of exercise did not translate to a greater improvement in functional status. These data point to the fact that oxygen delivery and utilization may be more important for quality of life than muscle strength in patients with COPD.

**Growth Hormone**

Similar increases in muscle strength and muscle size as those attained with testosterone replacement have been observed in older subjects receiving growth hormone therapy. In addition, growth hormone seems to be more effective on reducing fat mass than testosterone replacement. However, the side effects associated with the use of growth hormone include headaches, lethargy, joint swelling, pain, edema, arthralgia, carpal tunnel syndrome, glucose intolerance, and diabetes.

Growth hormone combined with strength training has not been demonstrated to have an additive or synergistic effect. Hennesssey et al. demonstrated that 6 mos of rhGH + progressive resistance training and placebo injections + exercise resulted in a 55.6 and 47.8% increase in strength, respectively, with no differences between the two interventions. Yarasheski and colleagues showed similar results with regards to increased strength with a combined intervention of rhGH + strength training in older men and also showed that progressive resistance exercise resulted in an increase in muscle protein synthesis that was not augmented by rhGH.

These studies demonstrate an effect of rhGH on fat free mass but a greatly increased risk of undesirable adverse effects. Because testosterone seems to produce similar result with regards to muscle and strength, growth hormone use to treat sarcopenia, and/or muscle fatigue should be discouraged. This is particularly true because growth hormone produces no additional effects compared strength training alone.

**Albuterol**

Albuterol (salbutemol) is a β2 adrenergic receptor agonist with anabolic effects although its effects have not been evaluated in many patient groups. Caruso et al. examined 9 wks of resistance exercise training and the use of albuterol (16 mg/day) or a placebo in healthy young subjects. Kinali et al. administered albuterol at 16 and 32 mg/day to patients with facioscapulohumeral dystrophy for 52 wks. They observed an increase in lean body mass of 1.57 kg as well as an increase in strength for the 32-mg/day group vs. 0.25 kg for the control group. Kinali et al. administered albuterol to children with spinal muscular atrophy for 6 mos and reported a 21.6% improvement in strength and a 20% increase in forced vital capacity as well as a 4.2% increase in lean body mass with few side effects. Uc et al. administered albuterol to underweight Parkinson’s disease patients at 16 mg/day for 14 wks. Symptoms of the disease were significantly improved by the intervention. Further, lean body mass was increased by 9.5% and thigh-muscle cross-sectional area was increased by 5.3%. One of the eight subjects receiving albuterol withdrew after 2 wks because of headache, jitteriness, and anxiety. Further, resting heart rate in the seven patients who completed the trial went from 78.3 to 85.6 beats/min. Thus, albuterol seems to be effective in increasing lean body mass, muscle mass, and strength in various patient groups. Further study of this agent in other patient populations is warranted, particularly when combined with strength training.

**Cancer Fatigue**

Although fatigue is an almost universal symptom of cancer, there are few studies that have examined its causes or treatment. A number of studies have shown that a large percentage of pa-
tients with cancer complain of chronic fatigue. Winningham\textsuperscript{152} wrote that the manifestations of fatigue are better appreciated “if fatigue is conceptualized as a syndrome, namely, cancer-related fatigue syndrome.” Patients and practitioners often mistake lack of sleep as a cause of cancer-related fatigue syndrome and often advise rest or increased sleep to alleviate this syndrome. Increased rest paradoxically can result in further deconditioning and exacerbate cancer-related fatigue syndrome. Lee and coworkers\textsuperscript{153} demonstrated that, compared with age- and gender-matched subjects, patients with lymphoma scored significantly lower on a variety of functional tasks, including a 6-min walk, a 50-ft walk, and forward reach. They also found a significant relationship between performance on these functional tests and score on a brief fatigue inventory, indicating that physical functional capacity is strongly linked to fatigue in these patients. Interestingly, even among breast cancer survivors, 5 yrs after treatment, reduced functional status is highly prevalent compared with age-matched controls.\textsuperscript{154} Patients with cancer who are most severely fatigued during treatment for their cancer remain fatigued well after treatment and even after resolution of their disease.\textsuperscript{155} Because of the persistence of cancer-related fatigue even after treatment and often after resolution of the tumor, metabolic and physiological adaptations such as deconditioning and cachexia may play a large role in this problem. Therefore, strategies to increase physical activity and decrease loss of skeletal muscle during treatment for their cancer should be strongly considered.

Kurzrock\textsuperscript{156} speculated that cytokines may play a role in cancer-related fatigue. Cachexia is present in almost 50% of patient with cancer and is characterized by loss of body mass and, in particular, skeletal muscle. This loss of muscle and body mass is not explained by reduced food intake alone, and has been associated with increased levels of cytokines such as interleukin 1 (IL-1), IL-6, IL-8, and tumor necrosis factor alpha.\textsuperscript{157,158} Elevated cytokines have been implicated directly in the etiology of fatigue. However, the accelerated loss of skeletal muscle is likely the primary mechanism by which elevated cytokines result in increased fatigue in patients with cancer.

As discussed previously causes of cancer-related fatigue likely fall into the following general categories: anemia, deconditioning, and weakness that may be secondary to cachexia or loss of skeletal muscle. It is quite likely that fatigue associated with cancer and its treatment involves each of these problems as well as anorexia/malnutrition, which also may lead to muscle dysfunction.\textsuperscript{159} Unfortunately, there have been no systematic examinations of the potential causes of cancer-related fatigue. The most frequent interventions to reduce cancer-related fatigue have been increasing hemoglobin levels through the use of rhEPO and/or exercise.

**Anemia**

Anemia is a frequent consequence of cancer and the use of chemotherapy as well as hemodialysis. These causes of anemia respond to the use of rhEPO, with a number of studies demonstrating significant improvements in Hb levels.\textsuperscript{160,161} The development of anemia in cancer patients and its subsequent treatment with rhEPO is strongly associated with quality of life. Two large, multicenter trials demonstrated that increasing Hb levels were associated with a significant improvement in “energy” level, activity level, functional status, and overall quality of life.\textsuperscript{162,163} These studies show a clear benefit of the treatment of anemia in enhancing quality of life and decreasing symptoms of fatigue. A recent review of literature\textsuperscript{164,165} shows a consistent effect of the use of epoetin alfa on improving quality of life in patients with a wide range of different tumor types. However, these studies used qualitative endpoints (questionnaire, self-reported fatigue) and no direct measure of functional status.

Although there are very few studies examining effects of both correcting anemia and exercise training in patients with cancer, there is evidence of improvements in functional capacity by increasing Hb levels in hemodialysis patients. Lundin\textsuperscript{165} demonstrated a 50 ± 0.9% increase in VO\textsubscript{2max} when rhEPO was used to increase Hb levels from an average of 7.1 ± 1.4 to 9.8 ± 2.1 g/dl in men and women undergoing hemodialysis. Metra\textsuperscript{166} also demonstrated a significant improvement in VO\textsubscript{2max} in severely anemic hemodialysis patient after use of rhEPO. Akiba\textsuperscript{167} described such a study in patients receiving hemodialysis. VO\textsubscript{2max} was first measured in anemic dialysis patients before and following treatment with rhEPO. The patients experienced a significant increase in aerobic capacity (approximately 20% improvement). The patients were then divided into a 3-mo aerobic exercise training and sedentary control group. Those patients assigned randomly to the control group demonstrated a decrease in VO\textsubscript{2max} (despite unchanged Hb levels), whereas those participating in exercise showed a significant and substantial increase in exercise capacity. These results demonstrated that the use of rhEPO can result in improved function, but some of the decreased VO\textsubscript{2max} and functional capacity seen in these patients was the result of inactivity.

In one of the few studies examining the effects of anemia and cancer on exercise capacity, Daneryd\textsuperscript{168} examined 108 selected cancer patients experiencing involuntary weight loss. They randomly assigned these patients to rhEPO or indomethacin
treatment. Although there was no difference in the rates of mortality between the two groups, the patients treated with rhEPO did not become anaemic and preserved their exercise capacity. The patients who did not receive rhEPO demonstrated a significant decrease in Hb and a concomitant decrease in VO2max and functional capacity. These investigators concluded that “the institution of early and prophylactic rhEPO treatment to patients with progressive cancer prevents development of tumor-induced anaemia. This achievement was associated with a better preserved exercise capacity, which is explained in part by improved whole-body metabolic and energy efficiency during work load.” This study demonstrates the importance of maintaining or improving Hb levels to prevent a decrease in functional capacity in men and women with cancer.

Central Fatigue in Cancer Can Be Successfully Treated Using Psychostimulants

Fatigue in cancer patients can be treated effectively using psychostimulants such as methylphenidate. This drug increases brain dopamine concentrations. Thus, the possibility exists that brain dopamine concentrations are reduced in individuals with cancer. Regardless, increasing brain dopamine concentrations has a beneficial effect on cancer-related fatigue. In a pilot study, Schwartz et al. reported that in cancer patients receiving interferon-α therapy who ingested 20 mg of sustained release methylphenidate and followed and exercise program 4 days/wk for (15–30 min/day) for 4 mos had a reduction in subjective fatigue and had better cognitive function than those individuals who exercised only and than a historical control group that received interferon-α therapy. Obviously, a weakness of this study is the use of a historical control group rather than a control group randomized and going through the interventions at the same period of time. Breithart et al. reported that the treatment of patients with HIV who had fatigue with 60 mg of methylphenidate or 150 mg of pemoline another dopaminergic agent resulted in reduced fatigue severity, improved quality of life, and reduced depression levels. Thus, based on these data in from patient populations with fatigue, the use of psychostimulants could have a beneficial effect on treating fatigue in individuals with cancer.

Anabolic Hormones

Few studies have examined the effects of androgens on body composition in cancer. Chlebowski et al. administered nandrolone decanoate (200 mg/wk for 4 wks) to individuals on chemotherapy who had advanced nonsmall cell lung cancer. They reported that half as many patients had weight loss on the anabolic hormone therapy compared with those patients not treated.

Aerobic Exercise Training in Patients With Cancer

Decreased levels of physical activity result in deconditioning, characterized by a decreased VO2max. Complete bed rest results in a rapid and profound decrease in aerobic capacity. Because one cause of cancer-related fatigue may be deconditioning and reduced levels of physical activity, there have been a few studies examining the effects of regularly performed exercise on functional status in cancer patients.

Dimeo and his colleagues examined the effects of aerobic exercise in hospitalized cancer patients. They recruited patients receiving high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation. Thirty-three patients were randomly assigned to a training program that consisted of interval type of training on a cycle ergometer while supine (30 min/day, 15 1-min bouts at 50% of maximal heart rate reserve with 1-min rest periods) and a control group of patients who performed no exercise. These investigators saw a 27% greater loss in performance on a treadmill in controls compared with the exercised patients. Interestingly, the investigators observed significant decreases in duration of neutropenia and thrombopenia, severity of diarrhea, severity of pain, and duration of hospitalization in the exercise group compared with control. Schwartz et al. examined the effects of regular exercise on self-reported fatigue in women (n = 72) with breast cancer receiving chemotherapy. They examined the effects of a home-based exercise over the first three cycles of chemotherapy and observed a significant reduction in fatigue that was related to compliance to the exercise recommendations. Segal et al. examined a large group of breast cancer patients (n = 123) and demonstrated that when compared with control (no exercise) and self directed and a supervised exercise program produced a significant increase in functional capacity and decrease in weight and fatigue.

Dimeo and coworkers examined a small number of cancer patients (n = 5); however, all of the patients who were studied reported suffering from severe fatigue for a time ranging between 5 wks and 18 mos and because of this fatigue they were hindered from performing normal daily activities. All of the patients trained on a motorized treadmill at an intensity that had been determined to correspond with a circulating lactate level of 3 mM for six consecutive weeks. This value roughly corresponds to the anaerobic threshold. As they
became better conditioned, their blood lactate levels began to fall during the training, the speed of the treadmill was increased. In this way the training intensity remained constant. The results were very instructive about the capacity of cancer patients to respond to aerobic exercise training. The training speed increased by 23% \((P = 0.06)\) and the distance walked per session increased by 100% \((P < 0.05)\). Maximal exercise performance was also significantly increased. The authors concluded that “cancer patients suffering from primary fatigue should not be advised to increase the amount of daily rest. Rather they should be counseled to carry out aerobic exercise . . .” These studies demonstrated the regularly performed aerobic exercise training is both safe and effective in patients with cancer whether they are receiving chemotherapy. Increasing the amount of time that a patient is in bed resting will very likely cause a further deterioration of VO\(_{2}\)max, anaerobic threshold and functional capacity, leading to an even greater feeling of fatigue. Windsor and coworkers\(^\text{180}\) randomly assigned men with prostate cancer receiving “radical radiotherapy” to a control group who were given the advice to rest when they were tired compared with a group who were advised to participate in an aerobic exercise program consisting of walking 3 days/wk, 30 min/day, 60–70% of calculated heart rate maximum) and measured treatment related fatigue. They found a significant increase in the ratings of fatigue after only 4 wks of treatment in the control group with no change in fatigue in those men participating in the exercise. They noted that “improved physical functioning may be necessary to combat radiation fatigue.”

Aerobic capacity is a strong predictor of the level of fatigue in patients with cancer.\(^\text{181}\) In patients with nonsmall cell lung cancer, VO\(_{2}\)max is an independent predictor of postoperative complication following lung resection surgery.\(^\text{182}\) Six of seven patients with a VO\(_{2}\)max/kg body weight less than 60% of predicted, but only 8 of 65 with values >90% of predicted, exhibited postoperative complications. Anaerobic threshold (exercise tolerance) was found to be an independent predictor of postoperative mortality in patients with lung cancer.\(^\text{183}\)

Kolden and coworkers\(^\text{184}\) examined the effects of a group exercise program consisting of flexibility training and approximately 20 mins of aerobic exercise 3 days per week for a total of 16 wks in women (mean age of 55.3 ± 8.4 yrs) who had been surgically treated for stage I, II, or III breast cancer. They observed an increase in quality-of-life perception as well as VO\(_{2}\)max and strength.

**Summary**

As stated previously, fatigue is physical and/or mental weariness resulting from exertion, that is, an inability to continue exercise at the same intensity with a resultant deterioration in performance. The physiological mechanisms for this fatigue may be related to a number of physiological and metabolic parameters. An understanding of these parameters is essential if fatigue is to be addressed in a systematic way. Fatigue from exertion may be related to deconditioning (decreased maximal cardiac output and/or reduced muscle perfusion or oxidative capacity), reduced muscle mass or muscle quality, anemia, poor oxygen extraction, poor nutrition or malnutrition, or any combination of these factors.

Aerobic exercise and strength training regimens have been used to improve functional status and reduce fatigue that has been associated with advancing age and/or an existing chronic disease or condition. CHF, COPD, and end-stage renal disease are associated with accelerated loss of muscle and fatigue. Both cancer-related fatigue and cancer-associated pain have physiological causes and are treatable. Pain management in the treatment of cancer is a standard component of cancer therapy, while management of fatigue is not considered the standard of therapy. Despite an overwhelming body of evidence that demonstrates improved quality of life and decreased fatigue after treatment for anemia, the treatment of anemia in cancer is less a therapy for fatigue and quality of life than a prophylaxis against transfusion. Fatigue and cachexia related to cancer and its treatment results in long-lasting, persistent fatigue. Comprehensive therapy for cancer related fatigue should included exercise along with nutritional and pharmacological therapy. It is unlikely, for example, that any patient will be able to participate in even a low intensity exercise program if he is anemic.

It also should be recognized that regular aerobic exercise and progressive resistance exercise have different effects. Loss of muscle mass in response to cachexia or inactivity should be treated with resistance exercise training along with any antitumor therapy. On the other hand, decreased VO\(_{2}\)max that is secondary to anemia and deconditioning should include regular aerobic exercise such as walking. There is not a single published study examining the effects of exercise in patients with cancer that has reported a negative result. “Cancer rehabilitation” programs to comprehensively treat fatigue should be the standard of care. Just as the common advice to those who had suffered a myocardial infarction had been bed rest has now changed to early and vigorous cardiac rehabilitation in these same patients, exercise may have a powerful effect on fatigue and fatigue related symptoms in those with cancer. Additional cachectic conditions resulting from heart failure, COPD, and hemodialysis should be treated with a compre-
hensive battery of therapies designed to reduce fatigue and increase functional status and quality of life.

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Muscle Pain Syndromes

ABSTRACT


This article summarizes the evidence for two major clinical syndromes of muscle pain: fibromyalgia and myofascial pain syndrome. The evidence for diagnostic and treatment approaches is reviewed.

Key Words: Musculoskeletal, Pain, Fibromyalgia, Myofascial Pain

Pain from muscle (and its surrounding fascial tissue) is one of the most frequent diagnoses seen in general practice and in pain clinics. References to pain resulting from palpable and tender areas in muscle began to be found in European medical literature in the early 1800s. Virchow coined the term “muscular rheumatism” in 1852 to describe palpable changes in muscle as a complication of rheumatic fever. In the early 1900s, Gowers discussed musculoskeletal pain in a variety of conditions, including lumbago, which he thought was caused by inflammation, and coined the term “fibrositis.” Stockman was concurrently discussing connective tissue hyperplasia, which came to be an early hypothetical pathophysiology of the fibrositic condition. Kellgren was the first to report referred pain during palpation of tender points in the muscle.

In the latter part of the 20th century, with the superb work of Travel, Simons, and Gerwin on myofascial pain syndrome (MPS), the work of Wolfe, Yunus, and Bennett on fibromyalgia (FM), and the efforts of many others, clinicians began to entertain a distinction between these two muscle pain syndromes. Travel taught of a posttraumatic, regional pain disorder associated with painful areas which, when palpated, triggered a sensory phenomenon (referred pain) into anatomically distinct areas. Fibrositis, and later FM, was characterized as a more systemic process, often associated with sleep disruption and sometimes with affective diagnoses. Travel and Simons corroborated the distinction between the two syndromes although, to date, there is no formal criteria for making this diagnosis. FM passed through several temporary criteria until 1990, when the American College of Rheumatology codified a formal taxonomy and diagnostic scheme to be used for epidemiology and research. Unfortunately, it has become common practice to use it as if it were a definitive diagnostic criteria. Currently, MPS is numerically the foremost primary muscle pain disorder, whereas FM is now thought to be part of a spectrum of diseases characterized by systemic symptoms, with the muscle pain (formally, “muscle tenderness”) probably representing a secondary manifestation of central sensitization.
Muscle pain from rheumatologic causes (autoimmune processes, such as polymyalgia rheumatica) is prevalent and can be very disabling, but it is beyond the scope of this article, which will focus on nonrheumatologic muscle pain syndromes.

**Diagnosis**

A major impediment to the development of specific, distinguishing diagnostic criteria has been the ongoing debate over the validity of MPS and FM as bona fide syndromes, and over the extent to which MPS is distinct from FM. Despite continued and sometimes emotionally charged debate, numerous previous studies have suggested that there are two distinct entities in muscle pain: the systemic, hurt-all-over process FM and the more regional MPS. Results from a survey of practitioners in the American Pain Society show that 88% believe that MPS is a distinct, legitimate clinical entity, and 86% indicate that MPS is distinct from FM syndrome (FMS).19

The process of developing criteria for FM also has proven to be important in distinguishing it as a specific entity. Early proposals for diagnostic criteria for FM11 stimulated increased study of the then-misunderstood and underresearched syndrome and led to increased acceptance of its clinical validity. This research eventually led to the development of formal, consensus-based diagnostic criteria, which were then subjected to experimental validation and were ultimately officially endorsed by the American College of Rheumatology (ACR). Although there are problems with the ACR criteria, they have provided an important framework for communication and research regarding FM. The lack of such a widely accepted and criterion-based diagnostic scheme for MPS has been deleterious to clinical communication and research. Our MEDLINE review of the literature published since the classic Travell and Simons work7 indicates no successful, comprehensive, consensus- or empirically based effort to determine clinically valid diagnostic criteria for MPS. Comprehensive efforts to develop these criteria, like those used in the case of FM, would likely facilitate communication and more generalizable research regarding MPS, and would ultimately lead to improved diagnostic accuracy and more precise treatments.

**Diagnosis of FM**

The publication of the ACR criteria for diagnosing FM was a great step forward in our efforts to understand the syndrome. Unfortunately, the potential promise has never been fully realized, and there are many problems with the criteria. There is nothing that has proved to be specific about the 18 points selected, and this was simply the most recent scheme of several, all using other points. These points may be tender in normals and have not been shown to be externally valid (specific).13 The criteria are based on the patient’s subjective response to a nonspecific stimulus, and a biased operator then must assess this response. There is no possible way to blind either the subject or the examiner, and the locations of the points are readily available to the lay public over the internet. The whole diagnostic system rests on the palpation of these 18 points with finger pressure of approximately 4 lbs/cm²; of course, there are problems with inter-rater/examiner reliability. This situation has been helped some by the use of mechanical devices that quantitate this stimulus (the dolorimeter). To say the least, these criteria are subjective and nonspecific and are predictably quite controversial. This lack of specificity comes with many perils, particularly that of overdiagnosis. The less astute clinician may abandon the differential search for the many other causes of widespread pain prematurely (such as polymyalgia rheumatica, statin side effect, growth hormone deficiency, hypothyroidism, parasitic diseases, Lyme disease, to mention a few), with the obvious incumbent danger to the patient. The only prudent approach is that FM must remain a diagnosis of exclusion.

Now, a process of empirical validation of these criteria must occur. On the basis of experience in development of the International Headache Society criteria and psychiatric diagnoses by the Diagnostic and Statistical Manual, the starting point in the criteria development process should be to establish a broad clinical consensus regarding the signs and symptoms that comprise FM. The next step in this process is internal and external validation of the signs and symptoms designated as experimental FM diagnostic criteria.

Internal validation uses statistical pattern recognition techniques, such as factor and cluster analysis, to examine interrelationships between signs and symptoms and can help guide criteria development. External validation of proposed criteria should also be conducted, focusing on the ability of proposed FM diagnostic criteria to discriminate between MPS and other nonmyofascial conditions (e.g., neuropathic conditions).

There is accumulating evidence that the points selected by the ACR are not specific and that considerably fewer points may be sufficient to make the diagnosis. Patients with FM have shown decreased perception threshold for cold pain, threshold for heat pain, tolerance for cold pain, heat pain tolerance, aberrations of cold perception, abnormal thermal windup and, after sensations, a decreased spinal nociceptive flexion reflex threshold, and an abnormal summation of mechanical stimuli. Gracely et al.
also has shown evidence that there is augmenta-
tion in cortical and subcortical areas. Therefore,
this research which suggests FM is a central sen-
sitization disorder, as well as our work on the
tender points, suggest that there is likely no need
to test all 18 points. Perhaps a smaller number of
points in all four quadrants would be sufficient to
detect this central nociceptive sensitization syn-
drome with good sensitivity and specificity. Our
research indicates that as few as three sites may
provide enough information for differentiation
with normal subjects. Petzke et al. reports that
three paired sites may be sufficient. A logical start-
ing point for future validation research may be a
single representative point in each body quadrant.

FM was traditionally thought to primarily af-
flict women, and it certainly is diagnosed more
frequently in women than men. The prevalence
occurs in a 9:1 female:male ratio. MPS probably
occurs as often in men as in women if accounting
for the slightly increased occupational hazard in
men (i.e., heavy construction jobs).

Research Critique

Although the establishment of the consensus-
based diagnostic criteria greatly helped in improv-
ning and promoting research in FM, the subjective
nature of the criterion for this diagnosis makes for
potentially heterogeneous research populations
and difficulty with identifying interventions that
show statistical effect for the whole group, but that
may work perfectly well for subsets. It is also dis-
appointing that no other criterion (i.e., insomnia,
depression) have been assessed, and that the ACR
criteria has never been empirically validated.

Diagnosis of MPS

The idea that myofascial pain is a distinct pain
syndrome was first formally recognized in the sem-
inal work of Travell and Simons, and these au-
thors’ diagnostic guidelines based on identification
of trigger points have been published. The Classi-
fication of Chronic Pain, published by the Interna-
tional Association for the Study of Pain’s task force
on taxonomy, provides no specific criteria for the
diagnosis of MPS; rather, it offers the note that
diagnosis depends upon the demonstration of a
trigger point (tender point) and reproduction of
pain by maneuvers which place stress upon prox-
imal structures or nerve roots.

As described by Travell and Simons, MPS is charac-
terized by the presence of regional pain and the
presence of defined, exquisite painful trigger points
in a taut band of muscle, which produce characteristic patterns of referred pain
upon palpation and a local twitch response to me-
chanical stimulation or needling. Work regarding MPS by these and other authors
has also described numerous other signs and symp-
toms as being common characteristics of the dis-
order (e.g., ropiness in muscle, weakness, spasticity
etc.).

Test procedures, such as pressure algometry, sedimentation rate, myoglobin
levels, thermography, EMG testing, and response
to trigger-point injections or spray-and-stretch
treatment have been proposed as helpful in making
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At present, research suggests that spontaneous end plate noise on electromyographic examination may be a defining characteristic of myofascial trigger points, with no such noise noted in normal muscle or latent trigger points. Although these data strongly suggest that spontaneous end plate noise may ultimately prove to be a gold standard against which bedside diagnostic criteria for MPS can be validated, there is not yet total agreement on whether this characteristic pattern is necessary and sufficient to identify the trigger points of MPS. It is clear that endplate potentials are common in subjects with MPS in the affected muscles, but not exclusively so. The Rabbit Model of MPS is serving to better research this endplate noise as a potential diagnostic test. There is also some very interesting work sampling the micromilleu of the trigger points, with some potential utility from a diagnostic perspective. Shah et al. found that there was a significant elevation of inflammatory mediators (e.g., bradykinin), catecholamines (serotonin, norepinephrine), cytokines (tumor necrosis factor-alpha and interleukin-6 beta), and neuropeptides (substance P, calcitonin gene-related peptide) in trapezial trigger point of patients with MPS, vs. age- and sex-matched control subjects.

Consequently, there is not yet a consensus regarding a definitive/objective reference point (gold standard) for ensuring that any MPS diagnostic criteria are valid; however, the work of Simons and Shah hold promise in this regard, as well as the possibility of eventually elucidating the pathophysiology. As long as MPS is considered a syndrome, all relevant signs and symptoms should be included in any diagnostic criteria for the disorder. However, if an unequivocal pathophysiology of MPS is identified, then the disorder would no longer be a syndrome, and the name should be changed to reflect the specific pathophysiological mechanism accounting for the disorder. If the disorder proves to be a specific dysfunction of muscle alone (i.e., electrodiagnostic changes at endpoints in trigger points), then a separate diagnostic classification would need to be generated for pain syndromes involving fascial tissue (e.g., tendons, ligaments, scars). Furthermore, even if electrodiagnostic or biochemical abnormalities prove to be a gold standard for identifying MPS, there will always be an important need for bedside tests to identify patients appropriate to refer for confirmatory and perhaps expensive testing.

Although developing adequate diagnostic criteria in the absence of such a definitive reference point may be challenging, criteria for the diagnosis of headache (International Headache Society) and psychiatric disorders (Diagnostic and Statistical Manual IV) have been successfully developed within this same context. Therefore, even in the absence of a gold standard for MPS, it should be possible to develop clinically useful criteria for diagnosis of MPS. Additional research to validate such criteria will be necessary. If spontaneous endplate noise and spikes are proven to be the defining characteristic of MPS, this will greatly facilitate validation research. The emphasis should be on developing user-friendly criteria that can be easily applied at the bedside without any special equipment.

The most significant problem with the criteria is its complete reliance on a patient’s subjective response to a nonspecific stimulus, which is assessed by a biased operator. The patient’s response to palpation is probably influenced by many psychological and sociological factors. There is currently no viable method to blind either the subject or the examiner. In summary, these criteria are subjective, nonspecific, and are predictably quite controversial.

Research Critique

Research in MPS and related musculoskeletal problems is essentially at a standstill because of the lack of common, standard diagnostic criteria. The process of survey consensus development, empirical validation, and revalidation are very clear. The passive acceptance of traditional, vague diagnostic schemes with no evidence base to support them is essentially the largest impediment to progress in this and all areas of pain research.

Treatment of FM

FM is a disorder characterized by widespread pain with point tenderness at defined areas and is often associated with sleep disturbance, fatigue, and morning stiffness. Although a variety of therapies have been proposed, empirical research indicates that the most effective therapies are consist of sedative therapy (analgesic serotonin/norepinephrine reuptake blockers), patient education, and aerobic exercise. Some patients can improve substantially just using these basic techniques, but the majority will need a more comprehensive rehabilitation approach.

Physical Therapy

Beginning with small, gentle active therapies by the patient, the physical therapist can help the patient begin to extend range of motion and flexibility through mostly active gentle activities. If the patient has kinesophobia, then cognitive behavioral techniques could be undertaken in conjunction with exercise to demonstrate to the patient that movement does not necessarily lead to entirely negative consequences.

Gradually increasing strength and flexibility to prepare for an aerobic program is the goal, and this...
is accomplished by a series of land and water exercises and devices (i.e., Swiss balls, Thera-Bands, etc.). The physical therapist is also actively involved at this stage in gait training and postural correction. Active, self-management techniques are the sine qua non of therapy. On the basis of our experience, electrostimulation modalities occasionally may have some use, whereas other passive techniques, such as ultrasound, diathermy, or massage are less effective and of no real lasting benefit.

Probably the single most important and effective therapy in FM is aerobic exercise. We recommend at least 20 mins of target heart rate (80% maximum) a day. It does not matter what type of exercise the patient chooses to achieve this aerobic state; often, the challenge is to encourage and motivate the patient to slowly reach this goal. A coordinated team approach is justified to help the patient through the inevitable discomfort, fatigue, and predictable setbacks. Mechanisms accounting for the effectiveness of aerobic conditioning are unclear, although several speculative mechanisms have been proposed. For example, one known effect of aerobic exercise is an increase in endogenous opioid activity. Enhanced endogenous opioid activity is associated with analgesia, and it is possible that this enhanced endogenous opioid activity may account for reduced FM symptoms after aerobic training. Other authors have proposed that aerobic conditioning may result in symptom improvements by increasing the resistance of muscle to potentially painful microtrauma from daily activity.

Although studies have documented that patients with FM are deconditioned relative to non-patient control subjects, no prospective studies have examined treatment-related changes in objective indices of aerobic conditioning as they relate to changes in FM symptoms. Although direct conditioning-related changes would seem to be the most parsimonious explanation for the effectiveness of conditioning-based treatment, an empirical test of this assumption is necessary to rule out the possibility that a factor other than conditioning may account for the observed changes.

We conducted a study that evaluated the impact of a home-based aerobic conditioning program on symptoms of patients with FM and determined whether changes in symptoms were related to quantitatively assessed changes in aerobic conditioning and if patients were likely to benefit from a self-managed, home-based aerobic program. The aerobic conditioning program took place at the participants’ homes, outdoors, or at a local fitness club at the discretion of the individual.

Twenty-six male and female sedentary individuals ages 25-59 yrs diagnosed with FM syndrome before baseline evaluation using the criteria established by the American College of Rheumatology participated in an individualized 12-wk, home-based aerobic conditioning program promoting an ultimate goal of daily aerobic exercise of 20–30 mins at 70–80% estimated maximum heart rate. Subjects were evaluated at baseline and exit for physiologic level of aerobic conditioning (VO2max), myalgic score (pain pressure threshold of FM tender points), pain ratings (McGill Pain Questionnaire–Short Form, Present Pain Intensity, Visual Analog Score), and a variety of psychometric tests.

Patients who completed the 12-wk exercise program demonstrated an increase in aerobic conditioning and a decrease in pain measured by the McGill Pain Questionnaire–Short Form. Importantly, patients who were unable or unwilling to complete this aerobic conditioning program reported significantly greater pain and greater disability from pain at baseline than those who completed the program. Patients suffering from FM can experience decreased pain and physiologic benefits from an aerobic conditioning program; however, patients who are experiencing significant disability from their pain are not likely to maintain a home-based conditioning program and should consider a group program. The results for passive physical therapy techniques (massage, ultrasound, low velocity manipulation etc.) are not encouraging.

**Occupational Therapy**

The occupational therapist (OT) takes the lead in functional restoration and works closely with the patient to prepare for the all-important aerobic program. The OTs also begin with gentle active movements and preliminary desensitization techniques. Later, the OT will optimize ergonomics, gait, work, sleep, and play postures, and help strategize with the team over the hurdles to functional and aerobic activities.

**Recreational Therapy**

Often, the recreational therapist is the first clinician to be able to get the patient to move freely and with some pleasure. In the context of restoring the patient to a pastime or a game that they once enjoyed, it may be possible to break through the kinesophobia and deactivation that so often accompany FM. With assistive devices and creativity (such as coaching instead of competing, bike instead of run, etc.), a patient can sometimes break the ice and find enjoyment and socialization in previously lost or new recreational activities.

**Vocational Rehabilitation**

As the patient progresses, the OT can begin to work with the vocational rehabilitation (VR) specialist to begin to assess and simulate work activ-
There are many medications that have been reported helpful in FM, but few that have been tested in double-blind, randomized controlled trials. At this time, a balanced empirical approach using observation, considering possible mechanisms, and then using the best current information to treat those mechanisms is the most productive clinical approach. Although monotherapy is the ideal, in practice, rational polypharmacy often is used. This requires a knowledgeable assessment as to general mechanisms and the specific mechanisms in any case, then combining drugs that make sense together (i.e., a peripherally acting agent with a centrally acting agent). Two basic classes of medications should be entertained; drugs used for prophylaxis (used daily to reduce the intensity, duration, and frequency of the pain) and abortive drugs (rescue agents) for crisis management.

The prophylactic drug selected often will be determined by the presentation of the patient. For example, if a patient with FM presents with significant depression, anxiety, and/or insomnia, the clinician could choose a tricyclic antidepressant with significant analgesic, sedative, and anxiolytic properties as a drug of first choice. The tricyclic antidepressants are traditional and seem to be particularly effective in FM, and a meta-analysis of FM treatments reports “antidepressants resulted in improvements on physical status and self report of FM(S) symptom.” This is likely the result of the serotonergic properties of the drugs, normalizing the putative serotonin deficit in FM, and the sedative properties of the class, normalizing sleep patterns. It is necessary that good clinicians have several tricyclic/quadracyclic drugs in their repertoire as they have varied side effects, which sometimes can be used to the patients’ advantage. Selective serotonin reuptake inhibitors have shown mixed results but have been disappointing for patients with FM in our clinical experience. Certain newer antidepressant agents, such as venlafaxine and mirtazapine, may show some promise, and very selective serotonin agents such as tropisetron (5HT3 antagonist) are showing some early success.

The antiepileptic compounds are some of the best studied drugs in neuropathic pain, but they have not been studied in patients with FM. Gabapentin has been studied in large randomized controlled trials in patients with postherpetic neuralgia and diabetic peripheral neuropathy. The mechanism of action in gabapentin may be of interest in patients with FM, however, it is not completely understood. It probably works primarily through enhancing natural gamma amino butyric acid systems in pain modulation, but it may also have some impact in suppressing excitatory amino acids such as glutamate, which may be associated with central sensitization. This may complement the effect of tricyclic antidepressants.

Skeletal muscle relaxants (SMRs) are a widely prescribed class of medications, but there is little succinct information about their pharmacology. They probably constitute an important component in the armamentarium of therapies for common conditions such as lower back pain, but are often prescribed in patients with FM with no evidence
as yet, and there is concern that long-term tolerance and long-term toxicity are unresolved to progress in nonpharmacologic therapies. Issues acute opioid protocol to allow the patient to begin increasing function and can use an acute or sub-acute opioid protocol to allow the patient to begin to progress in nonpharmacologic therapies. Issues of tolerance and long-term toxicity are unresolved as yet, and there is concern that long-term opioid use may actually elicit allodynia and/or hyperalgesia. The NMDA receptor antagonists (such as MK-801, ketamine, and dextromethorphan) have been considered for management of these effects but have proved to be too toxic for regular human use.

There are myriad other chemicals purported and hawked for the treatment of FM, such as nutraceuticals, homeopathic, and herbals. None have any evidence supporting their efficacy, and although most have low levels of toxicity, they can have a severely deleterious effect on our patients’ bank accounts. Acupuncture and other complimentary techniques have never been properly studied.

The key to successful treatment of the patient with FM is a trained, coordinated, and experienced interdisciplinary team using a functional restoration approach with a strong emphasis on aerobic conditioning and daily exercise. Creativity, compassion, and flexibility are essential. Some patients benefit from aerobic exercise and improved sleep alone, but most require rational-polypharmacy pharmacotherapy, intensified psychotherapy, or other elements of interdisciplinary pain management to make substantial progress.

**Research Critique**

Some minimal progress has been made in developing an evidence-based treatment of FM, but it is likely that a diagnostic criteria based entirely on patient subjective report will not provide specific enough targets for effective outcomes research. The great challenge of developing and using statistical methods appropriate for analyzing interdisciplinary methodologies simultaneously is also a significant hurdle. Cross-lagged, time series, and hierarchical models are available and may hold the key; newer technologies must be assessed and validated. The difficulties using standard randomized placebo controlled trials, which are suitable for drug studies, will need to be revisited: for instance, in the long-term trials that are necessary to assess nondrug therapies such as aerobic exercise, is it practical or even ethical to maintain a nontreatment wing?

**Treatment of MPS**

The more regional, posttraumatic MPS is treated differently and may respond to more local and specific techniques. The key ideas are relief of pain and inflammation, prevention of further injury, reducing spasm, correcting abnormal postures, and improving circulation.

**Physical Therapy**

The physical therapist should take the lead in the treatment of MPS. Acutely, more passive techniques such as ice or iontophoresis may be used. The use of ultrasound was found to be as effective as trigger-point injections in one trial. Splinting should be very brief and gentle, and active range of motion should be maintained as soon as medically feasible. When the patient moves into the subacute phase and starts to develop symptoms that are more consistent with a diagnosis of MPS, identification of behaviors/activities predisposing to ongoing injury must be identified and corrected. Postural imbalances, kinetic chain dysfunction, weakness, and spasm are all important targets for treatment. Although self-management is key, hands-on techniques such as massage and myofascial release can be important in treating subacute MPS. These should be delivered in a time-limited fashion, with the patient’s understanding that the goal is to move from passive to active therapies.

**Other Disciplines**

The role of OT is postural correction, ergonomics to avoid ongoing injury, and facilitation of the team goals. Psychology will target illness and maladaptive behaviors and often will work with VR to facilitate complete functional reintegration. Patients with MPS had higher scores for anxiety than depression, and appropriate cognitive behavioral therapy is traditional in most treatment centers. Therapeutic recreation and these other disciplines may have a role similar to that described previously for FM if the condition becomes more chronic. Low-level laser therapy has been used, but a meta-analysis “has no effect on pain in musculoskeletal syndromes.” Subsequently, a large open label trial was positive, so it is unclear whether this therapy has a role. Acupuncture often is mentioned for the treatment of MPS, but there is no compelling evidence as to its efficacy. One older large open-label trial of dry needling of the trigger point suggests efficacy. A later systematic review looked at 23 studies of which “no trials were of
sufficient quality or design to test the efficacy of any needling technique beyond placebo in the treatment of myofascial pain. Eight of the 10 trials comparing injection of different substances and all seven higher-quality trials found that the effect was independent of the injected substance. All three trials that compared dry needling with injection found no difference in effect.120

Medications
Nonsteroidal anti-inflammatory drugs have a prominent role in the management of MPS, particularly in those cases in which there is considerable inflammation.122,123 Certain drugs in this class may be more useful; these include ketoprofen, which has detectable antibradykinin and antiprostacyclin effects as well as the usual anti-prostaglandin effect. COX-2 inhibitors have not been tested specifically in MPS but can be useful in patients who have contraindications to or cannot tolerate nonsteroidal anti-inflammatory drugs. With long-acting nonsteroidal anti-inflammatory drugs and COX-2 inhibitors, these medications can be considered for prophylaxis of chronic pain, but the side-effect profile/risk of long-term use must be considered. Steroids can be particularly useful in the early/acute phases of MPS, particularly when there is significant inflammation. A short, tapering course of steroids may be indicated; however, longer courses have a questionable risk-benefit ratio.

Skeletal muscle relaxants are a widely prescribed class of medications used presumably to treat muscle spasm, the resulting postural abnormalities, and discomfort. They are very frequently prescribed for MPS, but there is little succinct information about their pharmacology, mechanistic rationale, or indication. As a class, they are structurally and pharmacologically diverse. Most of the research on SMRs is elementary and very old (often before the obsession with evidence-based medicine came into play), and there is little likelihood of any substantial research forthcoming, as they are all generic. Although these older studies have failed to show any one SMR to have greater efficacy than others, they have revealed significant differences in side-effect profiles. The literature (such as it is) does not support the superiority of any one agent over another.124

Metaxalone has the fewest reported side effects of any SMRs and seems to be the safest. Although cyclobenzaprine may not share the dangerous cardiac and neurological potential of its close relatives the tricyclic antidepressants, it does share other properties, particularly confusion, lethargy, and anticholinergic side effects. Carisoprodol presents the most significant concern, particularly because of its potential for dependence and abuse. Several investigators have called for carisoprodol to be classified as a controlled substance.124–128 There is one older RCT supporting the use of Clonazepam.129

At the other end of the side-effect/toxicity spectrum is carisoprodol, which continues to be heavily prescribed. A questionnaire study of physicians and patients revealed that although 95% of the physicians in the study were aware of the abuse potential of meprobamate, only 39% thought that carisoprodol had abuse potential, and only 18% were aware that it is metabolized to this controlled substance (meprobamate).130 Physicians should be aware of the full range of risks and benefits of this class of medications and be alert for patients with a history of chemical abuse, particularly barbiturates or benzodiazepines, and older patients with fall potential or those prone to oversedation or confusion.131 Skeletal muscle relaxants should be used only for the short-term treatment of MPS, and their use should be carefully monitored.

Trigger point injections with either local anesthetic alone, or with steroid are traditional treatments for MPS, interestingly without much evidence on which to base that legend.2,132 This embarrassing situation is actually not uncommon with regional anesthesia treatments in general.

Botulinum toxins are being used more often for treatment of MPS; however, the evidence base for this line of therapy is rather weak with small underpowered trials. The idea that trigger points represent focal areas of ischemia and necrosis, or that botulinum toxins cause relaxation of these ischemic area with improved blood flow, or that this has an impact on pain report has not been effectively investigated. Botulinum A toxin injection was equal to methylprednisolone injection in one small randomized controlled trial.134

Research Critique
Without standard diagnostic criteria, it is unlikely that any real progress will be made in pathophysiological, mechanistic, or intervention research in MPS. Clear, unequivocal, and published entry criteria for each trial will serve to improve this situation in the short term. Validation of statistically generated ‘proposed criteria’ should be funded, and performed.19 Larger and longer trials applying the well-known principals of biomedical research are needed.

Summary
Muscle pain syndromes are extremely common and are the most likely pathoetiology of chronic pain seen in any medical context today. There are two distinct types of nonrheumatologic pain originating from muscle: the regional, post-traumatic MPS and the less common whole-body FM. Although formal analysis of empiric techniques for distinguishing between these two are lacking, a familiarity with the ACR criteria for FM
and the works of Travell and Simons will allow the clinician to comfortably specify which is extant, at least in general. The research base is growing and improving in quality, yet there is considerable room for improvement. Better powered trials, more applicable outcomes, and more efficient statistical schemes are needed. The treatment schemes are partially distinct, with some significant overlap occurring if the syndromes become chronic. In that case, a thoughtful, balanced interdisciplinary approach is critical to a successful outcome. Aggressive cotreatment of psychological disorders is essential for success. FM occurs more frequently in women than in men, whereas MPS seems equally in either gender.

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Low-Back and Neck Pain Diagnosis and Treatment

ABSTRACT

Back and neck pain are symptoms, often complaints, and sometimes causes of disability, but they are not diseases. These distinctions are critical to understanding the personal and societal impact of back and neck pain and our opportunities to discover new ways to reduce their impact. This article briefly describes current diagnosis and treatment of spinal pain, the relationship between pain and disability, and the challenges in prioritizing our resource allocations between curing pain problems and reducing disability.

Key Words: Back Pain, Neck Pain, Rehabilitation, Disability

Back and neck pain are symptoms, often complaints, and sometimes causes of disability, but they are not diseases. These distinctions are critical to understanding the personal and societal impact of back and neck pain and our opportunities to discover new ways to reduce their impact. This article briefly describes current diagnosis and treatment of spinal pain, the relationship between pain and disability, and the challenges in prioritizing our resource allocations between curing pain problems and reducing disability.

Most people have episodes of low-back and neck pain periodically and in waxing and waning severity during their teenage and adult years. Reports of low-back pain prevalence range from 5 to 69%, depending on the survey period and severity criteria. Neck pain may be as common over a lifetime, if somewhat less prevalent during the short term. In either case, most people recover rapidly from acute pain episodes without medical intervention or significant incapacity. However, for those with pain persisting beyond the 3-mo maximum required for resolution of most musculoskeletal injuries in the arms and legs, resulting disability and health care demands constitute one of the major personal and public health problems facing adults worldwide. In the United States, 1% of the adult population is permanently disabled by back pain, and another 1% is temporarily disabled at a given time. Although the costs of neck problems have not been clearly reported, annual cost estimates for low-back pain and related disability in the United States exceed $50 billion.

There are important historical trends to consider. There is no evidence that the prevalence or severity of back and neck pain has significantly changed...
for many decades. However, between 1957 and 1976, back-related Social Security disability claims rose 14-fold in the United States. More current reports are conflicting but may show a positive trend. A recent survey of European and American social security systems concluded that the major impending problem is the increasing number of people older than 50 yrs in whom back pain is associated with long-term work loss, disability, and early retirement. By 2050, more than one in five Americans will be older than the age of 65. The aging of America must be considered both because of its potential socioeconomic consequences and because the relative frequency of various disabling pathologic conditions changes through the decades of life.

**Diagnosis: Finding the Source of the Pain**

The title of this report invokes the prevailing biomedical paradigm for back and neck pain. This model assumes that, with or without identifiable trauma, some initial biological event generates signals that are conveyed by peripheral nerves to the central nervous system. Here, the signals are processed in such a way that the person feels pain; “an unpleasant sensory and emotional experience.” Physical impairment and socioeconomic disability follow, commensurate with the severity of the pathology and pain. The primary health care mission in this model is to find the offending tissue or mechanism and fix it. This is also a key expectation of people with back and neck pain seeking medical care, as consistently reported to me in group interviews with thousands of patients with chronic spinal pain.

Anatomic sites within each functional spinal level with experimentally proven capacity for pain generation include external fibers of the intervertebral disc, various ligaments, vertebral periosteum, nerve roots or their dural sheaths, facet joints, muscles, and fascia. The gross pathologic mechanisms that disturb these structures often occur in the context of age-related degeneration of the discs and facets, particularly in the lumbar spine. Tears in the disc’s annulus may be painful or cause problems by allowing nuclear material to herniate into the epidural space, compressing nerve roots and inciting inflammation. It is less clear whether the often-observed entity called internal disruption of the disc causes pain directly, especially because the interior is relatively inert and without nerve supply. Combinations of osteophytic and soft-tissue hypertrophy of the facets and ligaments and bulging or protrusion of the disc may compress the nerve roots by causing stenosis of the central canal and lateral foramina.

Osteoarthritis of the facets may be painful. Vertebral body fractures can be painful. It is less clear whether acquired defects in the pars interarticularis cause pain, but subsequent forward slipping of the superior vertebra (lytic spondylolisthesis) and similar shifting due to incompetence of degenerating facets and discs (degenerative spondylolisthesis) can be painful. Ligament sprains can certainly be painful in the limbs, but the documentation of this mechanism in the spine is virtually nil barring severe trauma. Muscular pain is commonly thought to involve either strain or sustained contraction (spasm) that could be primary, secondary to, and protective against pain in an adjacent structure or generated through efferent mechanisms by psychosocial stressors. Fibromyalgia is a controversial syndrome in which widespread pain goes unexplained by other known entities. There are many explanatory models for the generation of pain in any of these spinal elements whereby abnormal mechanical loading is ascribed to the likes of leg length discrepancy, spinal malalignment, muscle or fascia dysfunction or imbalance, and abnormal posture with or without psychological input.

Beyond these gross pathologic conditions, much has been learned about cellular and biochemical activities at the painful site and the neural pathways through which pain signals are conveyed to and managed by the spinal cord and brain. In recent years, our knowledge of biochemical and cellular events at the site of nociception has expanded far beyond rudimentary descriptions of acute inflammation and cell-mediated immune responses to mechanical injury. Inflammatory cells release substances that sensitize and stimulate peripheral nociceptors that then produce a host of chemicals that excite primary afferent nerve cells. This excitation and pain signal transmission to the spinal cord are mediated or modulated by the likes of bradykinin, substance P, histamine, 5-HT, glutamate, cytokines, prostaglandins, and tumor necrosis factor. In the dorsal horn, transfer of the pain signal from afferent fibers to second order neural cells and cells ascending to the brain is further affected by a variety of neurotransmitters and neuropeptides such as amino acid glutamate and substance P. Second-order neurons may become sensitized, augmenting pain perception or continuing signal transmission to the brain after the peripheral nociception has ceased. Management of pain input within the brain is highly complex as manifested by recent concepts ranging from windup to neuroplasticity. The complexity of central nervous system processing is illustrated by an experiment in which people immersing their hands in cold water had more cingulate cortex activity on positron emission tomography scan when they believed the experience would be painful than under similar conditions in which they believed it would...
not be so painful. Further confounding the simple pain signal transmission from tissue to brain, there are descending positive and negative pathways modulating conduction through the interneurons at the spinal cord level. Descending information has been postulated as the mechanism through which psychosocial stress may produce pain in peripheral (muscular) tissues. In considering the current state of back and neck pain diagnosis, it is critical to keep in mind this complex system of pain communication between spinal tissues and the brain.

The traditional diagnostic tools available to the clinician caring for people with back and neck pain include the interview, the physical examination, laboratory tests, electrodiagnostic studies, and imaging with radiographs or magnetic resonance techniques. The first goal in the history and physical is to rule out suspicion of systemic diseases, especially cancer, infection and spondyloarthropathies. Also important is the identification of neurological complications, such as loss of strength, sensation, or bowel or bladder control, that might require urgent surgical decompression. Evaluation of psychosocial features that might affect care, therapeutic choices, and outcomes is appropriate here. However, the capacity of the clinical interview and physical examination to identify the painful tissue and mechanism is extremely limited, particularly in people with axial back and neck pain but no limb complaints implicating specific nerve root pathology.

In relevant guidelines and in common clinical practice, the decision to pursue diagnostic imaging is tempered by the facts that most episodes of back and neck pain improve without intervention (obviating the need for anatomic diagnosis) and that the prevalence of potentially pathologic lesions, such as disc herniation, osteoarthritis, spinal stenosis, and even the spondylolistheses, is high enough in asymptomatic people to create significant risk of false positive results for people in pain. In addition to static images designed to document gross pathology in the spine, recent attempts to identify which structures are causing a specific person’s pain have included provocative discography: injection of dye into the disc. It has been suggested that concordant pain distinguishes the culprit disc(s) from the other discs and spinal elements. Unfortunately, injection can produce pain similar to the patient’s complaint when the cause is known to be elsewhere, and 30–80% of people thought not to have same-level discogenic pain report pain with discography. Conversely, relief of pain by local anesthetic blockade has been proposed as a diagnostic approach to pain originating in facet and sacroiliac joints, pars interarticularis defects, and nerve roots. It is not clear that these injections have proven useful in directing care toward successful outcomes, possibly because of the confounding placebo factor.

Yet another approach to diagnosis goes beyond identification of specific anatomic and pathophysiologic sources to assignment within clinical classification schemes wherein patient types can be linked to treatment recommendations. These strategies may be as simple as distinguishing people with axial pain from those with associated limb pain, or they may require some clinical judgment, as in grouping people according to their pain response to repeated spinal flexion vs. extension. Ideally, people could be classified according to their likelihood of responding to available treatments.

For patients with persisting pain, lack of diagnostic specificity is perhaps a less-frustrating problem than inadequate sensitivity. The often-quoted 1982 synopsis of White and Gordon concluded that fully 85% of people with low-back pain go without a clear anatomic diagnosis. In 2001, well into the era of computed tomography, magnetic resonance imaging, and discography, Deyo and Weinstein stated that 70% of the 97% of people with low-back pain having no evidence of cancer, infection, metabolic, or visceral disease remain in the category of lumbar strain or sprain, admittedly “nonspecific terms with no pathoanatomic confirmation.” Nevertheless, the patient’s desire for a diagnosis is often compelling because it logically serves as the foundation for treatment, prognosis, symptom credibilidad, and disability and compensation decisions. Three recent reports are worth considering in this context, all of which show a lack of clinical benefit from taking magnetic resonance imaging scans either early in the course of an episode of low-back pain or in place of plain radiography ordered by the patient’s doctor.

**Treatment of Back and Neck Pain**

When considering the effectiveness of treatment, it is worth recalling that pain, as a subjective experience, is objectively unmeasurable. Chronic pain severity varies over time and is only loosely correlated (with few experimental exceptions) to physical impairment and socioeconomic disability. Despite a host of symptom and activity-based questionnaires and physical capacity tests developed in recent decades, definition of treatment success is multifactorial and highly dependent on the consumer or interpreter: the patient, the health care provider/system, the employer, and the insurance and compensation providers. These measurement issues make evaluation of treatment outcome difficult. As health care costs escalate, it is imperative that whatever benefits are produced by a given treatment are assessed in terms of their financial...
burden. All these problems with back pain outcome measurement contribute to a recent conclusion that “the literature is replete with conflicting results, modest effects and weak studies.”

Applying the biomedical disease model described in the section “Diagnosis,” treatment options may be organized according to pathologic taxonomy.

Herniated Intervertebral Disc

Many disk herniations do not cause pain, and those that do often resolve without specific intervention. For people with back and radicular pain suggesting disc herniation, oral and epidural medications and exercise, but not extended bedrest or traction, may provide some marginal benefit. When radicular pain is complicated by progressive neurological deficit especially with cauda equina syndrome, or persists for several weeks and imaging reveals a corresponding disk herniation, surgical decompression can be considered. In the best known trial of lumbar disectomy to date, patients who underwent surgery had greater pain relief in the first 4 yrs but probably similar results after 10 yrs. Microdiscectomy and open decompression both have advocates, but there is no clear advantage for intradiscal enzyme injection, or newer minimally invasive techniques.

Intensive exercise-based rehabilitation 4-6 wks after surgery may improve outcomes. Without evidence for regional variation in disk herniation prevalence, disectomy rates in the United States have been reported to be at least 40% higher than in any other country.

Spinal Stenosis and Degenerative Spondylolisthesis

Posterior decompression aims to relieve stenotic radicular and claudication symptoms, whereas fusion targets symptoms ascribed to accompanying spondylolisthesis or more subtle instability. Fusion seems to provide better outcomes than nonoperative care for at least a few years. Curiously, anatomic fusion does not always correlate strongly with short-term symptoms, although solid fusion may be associated with better long-term outcomes. Physical therapy, oral medication, and epidural steroid injection may be helpful, but clear evidence of efficacy from clinical trials is lacking.

Isthmic Lytic Spondylolisthesis

Flexion exercises and bracing can be helpful for moderate complaints. Surgical fusion may be the treatment of choice for people with chronic disabling back pain, although expectations of returning to strenuous activity may be unrealistic.

Idiopathic Low-Back and Neck Pain

Most people with back and neck pain have no clear anatomic diagnosis beyond the presence of age-related degenerative changes in the intervertebral discs and facets commonly seen in people without symptoms. In the acute phase of back and neck pain, anti-inflammatory and so-called muscle-relaxant medications, self-care exercises, and manipulation may have marginal benefit in reducing the severity and duration of pain. The vast literature on other treatments for acute spinal pain is inconclusive. It may be that for most people, reassurance and advice to keep active bring the best results.

For chronic axial pain, some benefit has been claimed for a wide variety of interventions including medications, injections, manual therapy, yoga, and acupuncture, but outcomes are overall unimpressive. For people with chronic back pain, surgical fusion techniques and intensive exercise programs with integrated behavioral support have drawn considerable attention. A Cochrane review of spinal fusion for degenerative lumbar spondylosis concluded in 2000 that there was no adequate scientific evidence for the efficacy of spinal fusion. Most of the trials reviewed did not have a nonsurgical treatment arm. Three trials comparing fusion and various forms of rehabilitation have shown small if any outcome differences overall. Despite our uncertainties about effectiveness, the National Inpatient Sample reflects a 179% increase in lumbar fusions per 100,000 people between 1990 and 2000, whereas hip and knee replacement rates increased only 13–14%. Recently, disk replacement surgery has been approved in the United States. The goal is to reduce presumed discogenic pain while preserving spinal motion and limiting the adjacent segment disease seen with solid fusions. Long-term results are not in, and caution has been advised, particularly in light of industrial pressures toward return on investment.

A Cochrane review summarizing 10 trials of treatments for chronic low back pain concluded that multidisciplinary, biopsychosocial rehabilitation aimed at restoring function improves chronic low-back pain and function, whereas less intensive interventions did not yield improvements in clinically relevant outcomes. There is limited evidence that people with disabling cervical pain do as well as their peers with low-back pain in intensive multidisciplinary programs. Some clinical guidelines now recommend multidisciplinary rehabilitation for patients with chronic low-back pain who have failed monodisciplinary treatments. Clearly, the identification of patients that are most likely to benefit from intensive multidisciplinary rehabilitation and the optimal content and intensity of re-
Beyond the Biomedical Model of Pain and Disability

By any measure, spinal pain and disability are gigantic personal and public health problems. In most cases, the anatomic cause is not known. The myriad and diverse interventions in common use have limited proven effectiveness in relieving pain. The biomedical diagnosis and treatment approach has probably been even less effective in reducing related disability. Spinal pathology correlates weakly with pain, as evidenced by more than one in four adults with no back pain having a herniated disc,

and the vast majority of people in pain having no clear anatomic diagnosis. Nearly all relevant studies demonstrate weak correlations between pain reports, measurable physical performance, and socioeconomic outcomes, including work capacity. The promise of biotechnology to reduce disability by preventing or curing the pain itself has not materialized. It is probably unreasonable to expect purely biotechnological interventions to reduce disability from back pain in the foreseeable future.

In recent decades, as disability compensation expenditures have increased and internal discrepancies have weakened the medical model, other explanatory models for disability have emerged. Social models hold that people are limited not so much by their impairments as by the ways in which society is organized to favor the able-bodied. In this context, solutions might be expected from social and political reform, such as the Americans with Disabilities Act, to ensure the rights and equal opportunities of people impaired by back pain. Economic models stem from the apparent dependency of disability rates upon ambient unemployment and the generosity and availability of relevant wage replacement or retirement programs. In cultural models, the population's collective beliefs and attitudes determine which forms of incapacity are compensable and to what extent.

Most recently, elements of all these paradigms have been integrated into disablement and biopsychosocial models. These models acknowledge that the progression from pathology to pain, impairment and disability depends heavily on the individual's personal attitudes, beliefs, and motivation and on surrounding social, economic and cultural influences. This perspective allows for individuals having very different disability outcomes from apparently similar clinical conditions. For example, a young person with a painful disc herniation and supportive spouse expects recovery and enjoys his office job, so he keeps working, yet another person with the same clinical problem retires on Social Security support when a doctor (or neighbor) tells him he may be crippled by returning to the heavy work he has always done.

So far, biopsychosocial models have had limited effect on clinical practice or social compensation policies relating to back pain and disability. However, they have inspired a new research initiative: the search for personal characteristics that predict disability. The hope has been that one may prevent what one can predict, if the predictive factors can be corrected. During the past decade, a multitude of studies have mustered lists of variables from expert sources and measured their associations with disability in samples of people with back pain, with and without a variety of clinical interventions. In some studies, the most strongly associated variables are collected and redirected at some of the entire original sample and predictive values are published. Unfortunately, the variables tend to be generic (job satisfaction, distress, physical exposures, disability exaggeration, self-concept) or demographic (age, gender) and do not inform intervention. There are no prospective studies in which disability has been significantly reduced by interventions targeting previously identified predictive personal characteristics.

Beyond this search for personal characteristics that might predict disability, there is growing interest in the meaning (thoughts, beliefs and attitudes) each individual develops for pain and how this meaning determines disability. Descriptions of this cognitive process range from how people match pain and impairment to fear of injury and more general references to coping. For example, Hadler claims that "the common denominator in all this choosing is a compromise in the wherewithal to cope." Self-concept, self-efficacy, and expectations can all have an impact on disability decisions and outcomes. After reviewing current models of disability, Waddell recently concluded that the decision to be disabled is to some extent a matter of personal responsibility and free will. The individual's assumption of this responsibility and an active role in choosing activity and social participation may be the crucial steps toward reducing disability. If the thoughts, attitudes, and beliefs of the person with the pain determine disability, they may well provide the key to reducing disability through educational interventions.

In the ideal biomedical educational scenario the lessons would be evidence based, clearly conveying best choices for particular clinical situations, and transmitted in convincing media to all stakeholders. A few decades ago this sort of program seemed achievable toward preventing disability from back pain. The leading explanatory model
for back pain and sciatica was the abnormal intervertebral disc and, logically, the best protection lay in reducing loads on the disc. Physical therapists could teach relevant biomechanical principles along with self-care exercises and help employers with jobsite modifications. This was the essence of the back school and ergonomic movements, which became very popular, but had no evident effect on disability.87,88

In the past decade, the lack of clear evidence indicating best interventions for specific medical conditions and the emerging focus on the role of the patient have inspired the development of shared medical decision making. Instead of the authoritarian doctor dictating the best treatment to the patient, there is a discussion of the options’ relative risks and benefits and subsequent treatment selection by the well-informed patient. As of yet, there are no evidence-based guidelines for discussing clinical evidence with patients in the process of making medical decisions.89 Generic educational interventions encouraging activity despite pain have met with equivocal results.89–93 In part, this may be the result of differences between what experts think should be taught and what people with pain want to know, as described in studies of educational pamphlet and clinical guideline use.94–96 Education is more likely to reduce disability if it is based on a solid understanding of the individual’s thoughts, beliefs, attitudes, and expectations regarding pain and activity.89 Adults resist learning under conditions that are incongruent with their self-concepts, and their openness to new information correlates with the degree to which the data relates to their specific problem set.97 A recent qualitative study of people with back pain and their health care providers concluded that “strategies should aim at training physicians in communication skills, especially about subjects for debate where patients’ beliefs and experiences color their expectations.”98 For instance it may be more effective to specifically address an individual’s spouse-supported fear of reinjury than to hand him a pamphlet describing clinical “red flags” or a video on therapeutic options.

Future Research Priorities

In 1980 the American Academy of Orthopaedic Surgeons, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the North American Spine Society convened a similar expert workshop. Their recommendations were exclusively pathology based, focusing on the dorsal root ganglion, inflammatory neuropeptides, vibration, disk cell phenotypes, muscle function, and the like.98 In 1995, the International Forum for Primary Care Research on Low Back Pain produced quite a different list of research priorities, including identification of clinical subgroups, disability reduction, psychosocial interventions, changing clinician and patient behaviors, and understanding patient beliefs.99

Reflecting on the discrepancies between these prior agendas, I recently surveyed the members of the International Society for the Study of the Lumbar Spine with an electronic query, “what single question about the diagnosis or treatment of back or neck pain would be most important to answer in the next ten years?” The Society has a juried membership of more than 200 people involved in spinal research, representing a variety of academic and practice disciplines, predominantly orthopedic surgery. Of the 44 respondents, the great majority31 felt that better diagnosis was paramount, with a critical internal schism (see Appendix). Approximately two thirds of these opinions pointed to better anatomic or biochemical diagnosis within the intervertebral segment. The remaining one third called for identification of subgroups of patients leading to better treatment prescriptions and outcomes.

In January 2005, a musculoskeletal research conference was arranged by the National Center for Medical Rehabilitation Research, the Interagency Committee on Disability Research, the National Institute of Arthritis and Musculoskeletal and Skin Disease, the Social Security Administration, and the National Institute on Aging. The musculoskeletal spine pain (nontumor) diagnosis and treatment section was charged with listing the key gaps in current knowledge, methodological issues, research priorities, and the level of research outcomes warranting funding. This group concluded that the key outcome criterion for future funding should be the potential of a given project to contribute to the goals of preventing and reducing disability from spinal pain. With these goals in mind, the priorities included better understanding of the psychosocial causes of spinal disability and how we can modify them, using translational research to explain and correct the fact that what we do know often isn’t used by people with spinal pain and their health care providers, and the division of people with spinal pain into valid and reliable clinical categories to better target interventions. Methodological recommendations included consider-
ation of all age groups in disability research, controlled intervention trials based on clinical subgroups using cost-effectiveness outcomes, and using both quantitative and qualitative approaches to understand the causes of disability from spinal pain.

Together, these expert agendas reflect the central challenge in prioritizing research initiatives for back and neck pain. On one end of the spectrum, there is the goal of preventing and relieving the symptom of pain by identification and treatment of the anatomic and biochemical mechanism behind it. At the other end lies the reduction of related disability by education and rehabilitation directed by better understanding of the operative psychosocial, economic and cultural factors. It is as unrealistic to demand that purely biological models eliminate disability as it is to expect social programs to relieve pain. The task before us is to decide where to commit funds and resources along this spectrum of challenges and opportunities.

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**APPENDIX**

1. What is the relationship between back or neck pain and the brain?
2. How can one tell whether the disk is the source of pain?
3. Can one prospectively identify individuals with acute low-back pain at risk for persistent symptoms who might respond to specific treatments, reducing disability/impairment?
4. What are the specific diagnoses giving different or similar kinds of low-back pain?
5. What is the source of pain (muscle, disk, fascia, ligament) in individuals with low-back pain?
6. How can we better diagnose microtrauma in spinal tissues in a minimally invasive manner?
7. Why are universites still training massive numbers of spine surgeons to perform ever more complicated surgeries when the “old-generation surgeries” were not effective and the new surgeries are more expensive and still ineffective?
8. How can we effectively modify degeneration of the spine?
9. Can subgroups of nonspecific low-back pain patients be reliably identified and more successfully treated with specific types of therapy?
10. How do the diagnostic components of pain (e.g., peripheral, central, psychological) relate to success in treatment with multidisciplinary management modalities?
11. How can we implement what we already know?
12. What are the underlying illnesses and mechanisms of back pain?
13. How can we find the pain generator?
14. Why are some degenerated disks painful whereas others are not, and how can we distinguish them?
15. What are the basic pathophysiologic mechanisms behind back and neck pain?
16. Where is back pain or neck pain coming from?
17. How does instability relate to back and neck pain?
18. What chemical change occurs in the degenerated disk to make it painful?
19. (It is impossible to formulate one question, given the risk of not addressing all aspects.)
20. Is sophisticated technology important in the diagnosis and treatment of back and neck pain?
21. Can we identify subtypes of back pain so that research, diagnosis, and treatment can be better directed?
22. How can we improve prevention of low-back and neck pain to indirectly diminish the burden on social security?
23. What is the structural explanation for nonspecific low-back pain?
24. What is the most scientifically valid and cost-effective treatment for low-back pain without a true radicular component?
25. What are the prognostic factors (e.g., anatomic, genetic, metabolic) for different treatments?
26. What is the biochemical basis of spinal pain: can it be identified by genetic analysis, blood tests, or emerging imaging techniques?
27. What novel diagnostic methodologies can be developed to characterize the source of pain in chronic back pain?
28. How can we localize the pain source and understand the pathophysiology?
29. What are clinically relevant subgroups of patients with back pain?
30. Can we simply use the existing paradigms of treating these problems and not pursue every case to the nth degree of imaging, accepting the natural history?
31. If fusion relieves discogenic back pain, why does it not relieve discogenic neck pain?
32. Why do people have differing disabilities for a similar cause of neck or back pain?
33. What is the mechanism and treatment of chronic low-back or neck pain?
34. Is it possible to classify low-back and neck pain patients according to clinical and/or other diagnostic criteria so as to provide specific treatments?
35. Can different varieties or subgroups of low-back pain be identified to find which interventions are most effective for which patients?
36. How can we link assessment, diagnosis, treatment, and outcome evaluation into a single framework?
37. How can the academic, economic and political powerbases surrounding spine disorders shift away from surgeons, who see only the smallest minority of patients?
38. Why are the links between back pain and spinal pathology so variable?
39. What personal beliefs about back or neck pain determine whether a person becomes disabled?
40. What is the role of disc degeneration in low-back pain?
41. What diagnostic test can segregate axial back and neck pain into clear categories that correspond to successful treatments?
42. What is the role of nerve degeneration and neuroinflammation in the pathogenesis of painful back and neck complaints?
43. Using modern diagnostic techniques, in what percentage of patients with chronic low-back and neck pain can a firm structural diagnosis be reached?
44. Why, given the extensive research, billions of dollars in funding, and dozens of logical treatments offered by thousands of doctors from virtually all specialties, have we not been able to impact the overall incidence or degree of disability associated with back pain? Do we require a completely new thought paradigm to attack this problem?
Musculoskeletal Problems as Comorbidities

ABSTRACT


Musculoskeletal comorbidities increasingly are prevalent and present specific research challenges and opportunities. Several definitions for musculoskeletal comorbidities exist depending on the patient population and research approach. Population studies document that musculoskeletal problems, defined as arthritis, are the most prevalent condition in the population as a whole and therefore a frequent comorbidity. As adults with disabilities age and as the population as a whole ages, musculoskeletal comorbidities will become increasingly common. Multiple research studies have begun examining the relationships of musculoskeletal conditions to other health conditions in pediatric, middle-aged, and older adults. Multiple specific research approaches are needed to understand predisposing risk factors, prevention, progression, consequences, and treatment strategies for these conditions.

Key Words: Musculoskeletal, Comorbidities, Research, Disabilities

The diverse realm of musculoskeletal (MS) health-related problems confronted by patients, their families, health care providers, and health care researchers is, simply put, vast. Concerns about MS health problems are growing considerably in rehabilitation, other medical fields, society, and the international community. The ongoing Bone and Joint Decade 2000–2010 and the World Health Organization (WHO)’s first global report, in 2003, on MS conditions are defining the scope of issues. More than 150 conditions are included in the WHO report alone. General population surveys, Medicare surveys, and smaller patient samples with specific diseases all yield high MS prevalence rates. This commonness, the varied course and severity of MS conditions (Fig. 1), and the frequently associated pain and loss of function challenge an evaluation of our knowledge of these problems as comorbidities.

From a clinical perspective, MS comorbidities relate to primary conditions in a number of ways. Four different situations exemplify some of the possibilities. First, a primary MS condition can cause a secondary MS condition, for instance, leg length discrepancy causing mechanical back pain. Second, a primary non-MS condition can cause a MS condition, for example, bone metastases in prostatic cancer or wrist arthritis in a patient using a cane after a...
stroke. Third, unrelated MS and non-MS conditions can affect rehabilitation of each other, for instance, hip fracture or joint-replacement rehabilitation in the patient with coronary artery disease or diabetes mellitus or stroke rehabilitation in the patient with rheumatoid arthritis. Fourth, in situations of many conditions, the MS condition simply adds to an already complex interacting set of conditions, for instance, osteoarthritis (OA) in the face of diabetes, cardiac disease, and dementia. These scenarios demonstrate the complex relationships among primary diseases or conditions and MS comorbidities.

This article, in contributing to defining needs in musculoskeletal rehabilitation research, takes a different approach from the others in this series. It provides a background literature review that bridges the geriatrics, physical medicine and rehabilitation, and other literatures. It provides examples of recent research approaches to the study of MS comorbidities and will conclude with suggestions for some core research themes. It therefore serves as an overview to contribute to the development of research of MS problems in relationship to other concurrent medical conditions.

Definitions of MS Comorbidity

Several definitions of comorbidity exist in the literature (Table 1). These include: (1) the concurrent presence of two or more chronic diseases or conditions; (2) (in people with disabilities) other medical conditions unrelated to the primary disabling condition; and (3) the coexistence of other conditions with a defined index condition. In looking for articles in a PubMed search for musculoskeletal comorbidities, one article referred to neck pain as a comorbidity in patients with low back pain. When is a MS condition a health condition in addition to some other totally unrelated primary health condition and, therefore, a comorbidity? When is it considered a primary problem, like the muscle spasticity in cerebral palsy, not as a comorbidity? What are the differences between a comorbidity, a secondary condition, and an associated condition—all terms used to describe conditions in aging people with disabilities and all possibly referring to body structures within the MS system? A recent chapter clarifies some of the history and current issues in this terminology.

Next, what components of MS comorbidities belong in a rehabilitation research agenda? One approach is to focus on topics dealing with the whole human being—whole body and person function and movement. Other considerations are the dimensions of health, both positive and negative, in the WHO International Classification of Functioning, Disability, and Health (ICF). These dimensions extend beyond the International Classification of Disease, tenth revision (ICD-10) codes for disease and condition etiologies (like osteoarthritis and osteoporosis). Part 1 includes impairments of body function and structure and associated effects on activities and participation. Part 2 includes environmental contributors and personal factors (see Table 1 for definitions). Research on MS disorders, and chronic widespread pain, has included both Part 1 and Part 2 concepts.

No single definition of comorbidity will be used in this review. A selection of the multiple
The current epidemiology of MS problems in several surveys shows an incredible ubiquity. The corollary is that MS problems are likely to be comorbidities in many patients. Arthritis is a specific group of MS conditions that have been broadly defined by the National Arthritis Data Workgroup to include entities like carpal tunnel syndrome, infectious arthritis, and systemic lupus erythematosus (see Appendix 1 for this listing). Arthritis, so defined, is among the most prevalent conditions in the United States. In 1997, 43 million persons had arthritis based on the National Health Interview Survey (NHIS) results, a significant 11% increase from 1990. These surveys included coding for one or more arthritic conditions. Depending on the definition of comorbidity, many of these indi-

### Table 1: Definitions

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<tr>
<td>Activity: execution of a task or action by an individual</td>
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<td>Age-related changes: changes in physiology and function believed to be inherent to the aging process and not to other factors like inactivity or disease progression</td>
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<td>Associated conditions: residual impairments from resulting from the defect, injury, or disease that has caused a disability (e.g., in cerebral palsy, seizures; in spina bifida, neurogenic bladder and bowel, mental retardation; in rheumatoid diseases, renal, cardiac, or pulmonary conditions)</td>
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<td>Body functions: physiological functions of body systems (including psychological function)</td>
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<td>Body structures: anatomical parts of the body such as organs, limbs, and their components</td>
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<td>Comorbidity: (1) concurrent presence of two or more chronic diseases or conditions; (2) in people with disabilities, other medical conditions unrelated to the primary disabling condition; (3) coexistence of other conditions with a defined index condition</td>
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<td>Disability: (1) inability or limitation in performing socially defined activities and roles expected of individuals within a social and physical environment</td>
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<td>Disability: (2) umbrella term in the ICF to indicate problems, i.e., impairment, activity limitation or participation restriction</td>
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<td>Disability: (3) (as defined in the Survey of Income and Program Participation) self-reported or proxy-reported difficulty with or reporting one or more of eight measures: (1) difficulty with one or more specified functional activities; (2) difficulty with one or more activities of daily living; (3) difficulty with one or more instrumental activities of daily living; (4) reporting one or more selected impairments; (5) use of assistive aids (e.g., wheelchair, crutches, cane, or walker) for &gt;6 mos; (6) limitation in the ability to work around the house; (7) limitation in the ability to work at a job or business (data for persons ages 16–67 yrs); and (8) receiving federal benefits on the basis of an inability to work</td>
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<td>Disease: (1) Morbus; illness; sickness; an interruption, cessation, or disorder of body functions, systems, or organs. (2) A disease entity, characterized usually by at least two of these criteria: a recognized etiologic agent (or agents); an identifiable group of signs and symptoms; consistent anatomical alterations</td>
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<td>Environmental factors: In the ICF, the factors that make up the physical, social, and attitudinal environment in which people live and conduct their lives; is a component of Part 2 of the ICF: Contextual Factors. Part 1 of the ICF deals with functioning and disability and classifies body functions, body structures, activities and participation</td>
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<td>Functional limitation: restriction or lack of ability to perform an action or activity in the manner or within the range considered normal that results from impairment</td>
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<td>Impairment: loss and/or abnormality of mental, emotional, physiological, or anatomical structure or function; includes all losses or abnormalities, not just those attributable to active pathology; also includes pain</td>
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<td>Impairments: problems in body function or structure such as a significant deviation or loss</td>
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<td>Participation: involvement in a life situation</td>
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<td>Participation restrictions: problems an individual may experience in involvement in life situations</td>
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<td>Pathology: interruption or interference of normal bodily processes or structures</td>
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<td>Personal factors: the second component of the ICF Part 2: Contextual Factors; these are not classified in the ICF because of the large social and cultural variance associated with them</td>
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<td>Secondary condition: (1) a condition causally related to a primary disabling condition and include decubitus ulcers, contractures, physical deconditioning, cardiopulmonary conditions, and mental depression; (2) impairments, functional limitations, disabilities, diseases, injuries, or other conditions that occur during the life of a person with a disability, in which the primary disabling condition is a risk factor for that secondary condition or may alter the standard intervention for prevention or treatment of any health condition (Syracuse Conference, 1994)</td>
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vials could possibly have been classified as having one, or two, MS comorbidities.

In the 1997 NHIS survey, 19% of the 43 million persons or 3% of the United States population reported that their arthritis contributed to a limitation in activities. Estimates are that by 2020 (in just 15 yrs) 60 million Americans may be affected by arthritic conditions. This prevalence doesn’t include information on how many of these individuals had other health conditions making the MS condition a comorbidity.

In the earlier 1989 NHIS, 16.4% of adults with arthritis reported that they had never seen a physician for the problem. These adults were more likely to have fewer health problems and no health insurance compared with those who did discuss their problems with a physician. Within this group, a substantial number had activity limitations. However, the majority had seen a physician at least once in the previous year. Therefore, many adults experience joint symptoms and yet do not discuss the problem with physicians.

In another population survey in 1999, disability information was collected as part of the Survey of Income and Program Participation to assess prevalence and associated health conditions in noninstitutionalized adults. Forty-four million Americans (22%), by this survey, reported having disabilities. The top two self-reported conditions, chosen from 30 possible, that adults identified as the main cause of their disability were arthritis or rheumatism in 17.5% and back or spine problems in 16.5%. The next highest cause was heart trouble or hardening of the arteries in 7.8%. Although cardiovascular diseases often are thought of as the most common category of health problem in the United States, these surveys indicate that when self-reported disability is present, MS conditions are the prevalent contributors. Whether these MS problems are comorbidities is not clear, but their high prevalence suggests a substantial number are.

Another population survey, the Behavioral Risk Factor Surveillance System, identified several other important characteristics of musculoskeletal problems. In a seven-state survey, 12–22% of the populations in these states had chronic joint symptoms (Persons who had chronic joint symptoms were defined as those answering “yes” to two questions: “During the past 12 months, have you had pain, aching, stiffness or swelling in or around a joint?” and “Were these symptoms present on most days for at least one month?”). However only 56–66% of individuals had their arthritis diagnosed by a doctor. Individuals may have seen other practitioners for their condition. Of those people who were diagnosed by physicians, 31–53% did not know their type of arthritis. Either physicians didn’t make a clear diagnosis to the patient or patients didn’t recall what they were told. Inadequate management and insufficient patient education, through self-management and other approaches, may be exacerbating a patient’s overall health. This is a possible risk, especially if a MS condition occurs in addition to other health problems.

Another important characteristic of people who report having arthritis is that leisure time physical activity is reduced compared with persons without arthritis. Because physical activity can improve arthritis-related symptoms as well as functional status, MS conditions, when present as comorbidities to other health problems, may be unnecessarily limiting the therapeutic benefits of physical activity.

**Health System Impact**

The health system impact of MS comorbidities is extensive. One study evaluated the impact of joint-related issues on physician visits, outpatient visits, and emergency departments. The principal diagnosis of arthritis and other rheumatic conditions (excluding disc disease and some other types of MS conditions) accounted from 5, 4, and 2%, respectively, of all visits. Problems in health care delivery for patients with musculoskeletal problems are beyond the scope of this work. One recent book, *When Walking Fails*, touches on many issues patients face when MS problems are associated with walking problems. The all-inclusive Mobility Mart dream solution cited in that book would address many of the clinical ramifications of MS comorbidities. Similarly, the creation of an outpatient MS practice for seniors (a gerontorheumatological outpatient service) is a newer approach to begin addressing the growing MS care needs in older patients with other comorbidities.

**Trends of Increasing Prevalence of MS Comorbidities**

The aging of the world’s population is a major factor in assessing the impact of MS problems in patients’ lives. The prevalence of arthritis in the NHIS surveys increase with age. The increased incidence with older age of some common musculoskeletal diseases, like OA and osteoporosis, may account partially for this. Another contributor to increased risk of MS comorbidity in the future may be the changes seen in aging MS tissue itself. As people age, the MS system may be more prone to injury from decreasing elasticity of connective tissue, decreased bone mass, changes in cartilage (easier fissuring and ulceration with weight bearing), and decreasing muscle mass. Actual studies of flexibility in older people are limited and needed.
Rene Cailliet, MD, a well-known physiatrist in his ninth decade, has had years of active clinical, teaching, and writing experience in MS medicine. In a recent interview, he still agrees with the clinical observations he wrote in his 1987 entertaining, and well-illustrated book, The Rejuvenation Strategy, written with one of his recently turned 50-yr-old patients. Among his conclusions were that the MS system starts significant aging changes at age 35. (Athletes must be especially aware.) Dr. Cailliet believes patients are able to make themselves feel younger physiologically—defined as more flexible, more agile, more energetic, stronger—even taller. Inactivity is a major source of patient’s MS problems. He advocates a practical approach to help patients feel better and younger through stretches, strengthening, walking, and relaxation.

Two areas of exercising and aging research are germane to Dr. Cailliet’s observations. Training for muscle power rather than strength alone may be more worthwhile clinically. Associations between muscle power and function are larger than between muscle strength and function. Preliminary research on the relationship of hip flexor range of motion in healthy older adults and gait suggest that loss of hip extensor range may be a significant, avoidable contributor to slower walking speeds in older adults.

Another trend that may lead to increased MS comorbidity could be the increasing emphasis on physical activity for good health. Individuals participating in sports and other leisure physical activities are at risk for MS injury. Understanding why and how these occur and whether they are comorbidities, strictly speaking, would contribute toward strategies to prevent musculoskeletal problems in individuals with significant other diseases or chronic conditions.

Sport-related injuries can occur with recreational (weekend warriors), regular, and elite athletes whether younger or older. These can be the result of intrinsic biomechanical abnormalities in the individual that become problematic with physical activity, like running. Extrinsic factors can include training errors, wrong equipment, improper techniques, and environmental issues. Other problems include overtraining that is associated with premature fatigability, emotional and mood changes, lack of motivation, and overuse injuries. Many of these athletes do not present to physicians with their symptoms and may limit their activity as a result of the injury or may recover from their injuries on their own. With aging, perhaps these same individuals will be at increased risk for musculoskeletal problems.

Health-related Quality of Life

Increasing consideration in measuring health care outcomes is being given to patients’ subjective experiences and their own health-related quality of life. Studies show that MS comorbidities contribute to poorer quality of life, highlighting another critical consequence of these comorbidities and their growing importance to patients.

Studies of Musculoskeletal Conditions Along with Other Diseases/Disabilities/Conditions

Pediatric Considerations

Children can experience a range of disabilities, many of which include MS conditions. In children with disabling conditions, problems like spasticity management are major issues. Children with traumatic brain injury are at especially high risk for MS problems. Depending on perspective and other health issues, these MS problems may be comorbidities needing improved understanding and management. MS comorbidities are more prevalent in female children and adolescents with posttraumatic stress disorder. A further review of the literature in this area will clarify other issues needing consideration.

MS Secondary Conditions

Studies have evaluated secondary conditions in people with disabilities. These secondary conditions have been defined as preventable health conditions causally related to a primary disabling condition. Chan et al. identified 66 such conditions, 21 of which were MS problems, including arthritis and pain problems in the spine and extremities. MS and medical secondary conditions were present in 40% and 50%, respectively, of the 1999 Medicare Current Beneficiary Survey respondents. Twenty-six percent of this population reported some level of disability. Generally higher numbers of secondary conditions were associated with greater disability. These conditions were coded as either primary or secondary ICD-9 diagnoses in billing data. Although not quantified, some of these MS conditions were secondary, rather than primary, diagnoses within the Medicare Current Beneficiary Survey. If these indeed were secondary billing diagnoses, these MS problems were comorbidities. From a research perspective, this study’s approach is a novel and creative way to study relationships of potential musculoskeletal comorbidities from administrative data sets.

Psychiatric Disorders With MS Comorbidities

MS problems often are considered primary problems or diagnoses in rehabilitation hospitals.
One recent survey in German orthopedic rehabilitation hospitals evaluated the detection rate of mental disorders in patients with neck and back pain, arthropathy, soft-tissue rheumatism, and other diseases. The detection rate (sensitivity) was only 48% and specificity 80%. The authors concluded that staff lacked the competencies necessary for making these diagnoses. In general, patients with MS diseases experience a greater prevalence of psychological distress. Given the critical importance of appropriate diagnosis and management of anxiety and depression, musculoskeletal problems are significant comorbidities associated with these psychological and psychiatric problems.

Pain

Pain is associated with many MS problems. In one recent population survey of adults ages 20–64, back pain was reported in 22.7% and shoulder pain in 21%. Further discussion of the pain component of MS comorbidities will be deferred for practical reasons only. It remains a critical component of any consideration of musculoskeletal comorbidities.

Comorbidity in Older Adults

The medical literature has established multiple relationships among comorbidities, function, and survival. Overall, comorbidity is associated with physical disability, higher health care use, multiple medications, poorer quality of life, increased adverse drug events, and increased mortality. Many Medicare patients have multiple chronic conditions. OA and osteoporosis frequently coexist. Current disease-specific practice guidelines do not account for the concurrence of these MS comorbidities along with other diseases. Optimal treatment approaches are not clear. In one hypothetical example of a 79-yr-old woman with chronic obstructive pulmonary disease, type 2 diabetes, osteoporosis, hypertension, and OA, 12 medications would be required along with a complicated nonpharmacological regimen.

These geriatric cases represent some of the most complex clinical situations in which the management of MS comorbidities is not straightforward and will need further research. Given the critical importance of pain control and maintenance of function, quality management of MS conditions may be a primary consideration in some patients, rather than a neglected, often by necessity, condition.

A recent longitudinal study evaluated the complex interaction of comorbidities, disability, and frailty. In the Cardiovascular Health Study, Fried et al. followed 5317 men and women 65 yrs of age and older for 4–7 yrs. Figure 2 illustrates the overlap of the separate concepts of comorbidities, disabilities, and frailty.

Comorbidity was defined as the presence of two or more of nine conditions: self-reported claudication, arthritis, cancer, hypertension, chronic obstructive pulmonary disease, validated diabetes (American Diabetes Association definition), chronic heart failure, angina, or myocardial infarction. Frailty was defined by the presence of three or more of the following

![Diagram of disability, comorbidity, and frailty overlap](image-url)
characteristics: weight loss, exhaustion by self-report, physical activity based on the short version of the Minnesota Leisure Time Activity questionnaire, walk time, and grip strength. The frailty phenotype was independently predictive (>3 yrs) of incident falls, worsening mobility or activities of daily living disability, hospitalization and death. It is impossible to isolate the contribution of arthritis, as a MS comorbidity, to decreased physical activity and slower walk times, and to frailty and its poor prognosis. Research on many fronts will be required to untangle the multiple interrelationships of MS diagnoses, disabilities, and frailty in older patients and to determine optimal preventive and clinical management approaches.

Because of the complexity in patients with multiple problems, of which MS issues are only one part, clinical and research models need to increasingly focus on individual patient goals. Focusing only on disease management is no longer viable. Fortunately, in rehabilitation, research will by necessity focus specifically on musculoskeletal components but also include, either simultaneously in some studies or separately in other studies, the issues beyond disease: function and some components of physical and social environments.

**MS Comorbidities in Stroke Survivors**

Two recent studies have specifically evaluated the prevalence of OA and its correlates with new onset stroke. One longitudinal study evaluated 236 stroke survivors within 2 wks of stroke onset (average of 8 days). Comorbidities were collected through self-report using a comorbidity disease index that was subdivided into eight general domains (cardiac, respiratory, diabetes, neurological (excluding stroke), cancer, vision, musculoskeletal (arthritis, osteoporosis), generalized symptoms). The average age was 70 (±11.8) yrs. The median number of conditions per person was two, and 39% of survivors reported having a MS condition. The additional analyses found no consistent patterns between individual comorbidity domains and functional outcomes. Interestingly, comorbid burden predicted independence in Barthel basic activities, IADL, and SF-36 physical function at 3 but not at 6 mos. These data show how comorbidities, including MS ones, may affect trajectories of stroke recovery.

A retrospective cohort analysis evaluated the presence of OA in stroke patients who received inpatient rehabilitation between 1994 and 2001 using the Uniform Data System for Medical Rehabilitation and the National Follow-up Services. OA was coded as present in 3094 (7%) of the 44,943 stroke patients. Despite a tendency for underreporting comorbidities in the Uniform Data System for Medical Rehabilitation system, the OA that was reported was associated with impaired stroke recovery. FIM scores were slightly lower at follow-up in stroke survivors with OA compared with patients without OA (97.7 ± 24.7 vs. 99.7 ± 24.9; P < 0.001). Inpatient length of stay was longer by 1.62 days (95% confidence interval [95% CI] = 1.15–2.08). For comparison, other comorbid conditions also affected length of stay. Two categories, that is, one to three conditions and more than three conditions, lengthened inpatient stay 1.49 (95% CI = 0.75–2.24) and 2.27 (95% CI = 1.54–2.98) days, respectively. However, these other comorbidities had no effect on overall FIM scores. The authors suggested that reasons for the longer length of stay, as well as slightly lesser recovery at follow-up, may include the presence of pain, impairing physical activity, and associated depression, anxiety, and fatigue that can be associated with pain and interfere with recovery. Unexpectedly, admission and discharge FIM scores were greater in patients with OA. The authors speculate that perhaps the greater use of aspirin in this population is associated with potentially an associated lessening of stroke severity. These data are among the first to document both the prevalence of OA in stroke survivors and its association with some poorer rehabilitation outcomes. Investigations into optimizing OA management in stroke patients are worthy of investigation.

**MS Disability in Other Medical Conditions**

Obesity is associated with a marked increased risk of OA, especially in the knees and ankles. OA also has an increased prevalence in non–weight-bearing joints in obese individuals. Metabolic effects may be affecting joints independently of weight-bearing status. Chest pain from mechanical problems in the back also occurs in obese people. Although as yet hard to achieve, weight loss is associated with a decreased risk of developing symptomatic OA. Because obese individuals frequently experience deconditioning from low levels of physical activity, progressive conditioning may result in overall improved MS function and lessened levels of MS pain problems.

One comprehensive evaluation of comorbid association with OA evaluated 11,375 patients ages 50 and older who had sought physician evaluation at least once for OA. Control subjects were 11,780 age- and sex-matched patients who had sought physician consultation for non-osteoarthritis conditions. Patients with OA had significantly greater levels of comorbidity than controls (odds ratio = 2.35; 99% CI = 2.16–2.55). Other MS conditions included other arthropathies, upper limb sprain, synovial and tendon disorders, and other joint disorders. These researchers also found a greater frequency of
obesity in the OA subjects compared with controls, as well as increased gastritis, phlebitis, diaphragmatic hernia, ischemic heart disease, and intestinal diverticula. Clearly these patients with OA have much more complex health and disability conditions compared with their non-OA counterparts. Researching relevant MS issues to understand the pathophysiology and treatment approaches in these patients must be thought out carefully and will be challenging.

Some MS disability may be closely related to a primary medical disease. In chronic gout, for example, 47% of 90 patients had MS disability.46 This disability was associated with presence of tophi, hypertriglyceridemia, and a history of ischemic heart disease.

Pain associated with some medical conditions may be the result of MS problems. For example, one project evaluated patients’ burden of symptoms among community-dwelling older persons with advanced chronic disease. Twenty-eight percent of patients with chronic obstructive pulmonary disease and 20% of patients with congestive heart failure reported having significant pain within the previous 24 hrs.47 These symptoms cannot be easily explained based on their primary diagnoses.

**MS Comorbidities in People with Disabilities**

People aging with disabilities are at risk for a myriad of MS problems. Life expectancy for persons with congenital disabilities and those with early-onset disability, like spinal cord injuries, are good.48 Currently, these 12 million people in the United States are the first generation to live into their later years. It seems that many of these individuals begin experiencing age-related changes 15–20 yrs before others of their same age without disabilities.49 Multiple types of MS issues arise in these patients, including pain problems as well as functional losses.7,49 In polio survivors, risks of joint pain, joint laxity, and muscle overuse are present. Neck, back, and shoulder pain are common in patients with spinal cord injury. In cerebral palsy, people can experience chronic overuse and atypical use of joints and muscles. These are associated with increased pain in some individuals.

The terms used for these various conditions may be somewhat confusing. The glossary lists the distinctions among secondary conditions, associated conditions and comorbidity. Regardless, these conditions represent musculoskeletal and associated functional changes that need to be studied, diagnosed, and treated within the entire context of the patient’s other health issues.

**Research Needs**

Research Areas Are Many:

1. Methodological issues around diagnosis, measurement, and approaches include basic diagnostic research criteria for distinguishing soft-tissue problems vs. joint dysfunction or arthritic conditions. Developing standard definitions of MS comorbidities may be necessary. Methodological challenges include the bidirectional nature of MS problems and health conditions. Some conditions, like obesity, lead to Ms comorbidities. In other situations, MS conditions themselves, like OA in patients with stroke, contribute to worsening problems associated with the primary problem.

2. Basic research on MS problems (etiologies, effects on body mechanics etc.) in the absence of other complicating illnesses will provide valuable information that is necessary to then better understand the effects of MS problems as comorbidities.

3. Epidemiologic natural history studies of aging and otherwise-healthy people, including studies of flexibility, are required to understand changes that occur within the MS system, associated pain, and effects on function. Similar longitudinal natural history studies are critical for high risk populations like children with traumatic brain injury. These studies will provide valuable baseline information on the frequency, type, and waxing/waning course of musculoskeletal problems in these populations.

4. Biomechanical studies of human function, like walking, are necessary to understand how to prevent, as well as treat, the consequences of MS comorbidities.

5. Prevention of MS comorbidities is important especially because MS problems are the most common problem affecting function in adults. Two concepts, written about by Cailliet and others, need specific research. One idea is that the well-conditioned musculotendinous system is less prone to injury. Is this always true? How well conditioned must the musculotendinous system be? Also, how is this conditioning best maintained as adults age? Specific research on appropriate exercises at the whole-person level is needed.

6. Rehabilitation treatments that are already identified as beneficial in isolated MS conditions need to be studied in their effectiveness in treating MS conditions when present with other diseases and health conditions.

7. Clinical studies of patients with complex and multiple conditions that include MS problems are necessary to identify feasible and cost-effective diagnostic and treatment approaches. This is especially critical in older adults with multiple morbidities and a cumulative burden of disease. Patients’ perspectives and priorities will need to be under-
stood. Their positive, as well as negative, adaptations to musculoskeletal problems, psychological and functional, in the presence of other health issues, need evaluation.

**Appendix 1: ICD-9-CM Arthritis Codes by the National Arthritis Data Work Group**

Abstracted from ICD-9-CM 1999 AMA Manual based on listing of codes in MMWR 2001;50:336. (Please refer to original sources. This is an overview only. Common sources of MS disorders in bold, common MS problems that are not classified as “arthritis” are in italics.)

### Synovial and Musculoskeletal Disorders

- **Arthritis**
- **Arthropathy**
- **Arthropathy Associated with Other Disease**
- **Arthritis, Rheumatic**
- **Rheumatism, Unspecified**
- **Other Inflammatory Polyarthropathies**
- **Osteoarthritis and Allied Disorders**

### Musculoskeletal Issues

- **Musculoskeletal Problems**
- **Musculoskeletal Morbidity**
- **Musculoskeletal Disability**

### Other Codes

- **Other Disorders of Muscle, Ligament, and Fascia**
- **Other Disorders of Synovium, Tendon, and Bursa**
- **Other Disorders of Joint**
- **Other Disorders of Connective Tissue**
- **Other Disorders of Joint**
- **Other Disorders of Periarticular Tissue**
- **Other Disorders of Muscle**
- **Other Disorders of Joint**
- **Other Disorders of Synovium, Tendon, and Bursa**
- **Other Disorders of Muscle, Ligament, and Fascia**
- **Other Disorders of Synovium, Tendon, and Bursa**
- **Other Disorders of Joint**

### References

12. Institute of Medicine, Executive Summary, in Pope AM (ed): Disability in America—Toward a National Agenda for Pre-