Chapter 4. Discussion

The goals of this review relate to examining the evidence in the medical literature for data that can guide policy for determining disability in patients with multiple sclerosis (MS). We found at least some evidence with which to address four of the five major topic areas. Although the literature in general and certain studies in particular suffer from limitations, reasonably strong conclusions can be drawn in some areas. The evidence for each topic is summarized below and is followed by a summation of knowledge gaps and recommendations for future research.

Discussion of Evidence

Reliability of Criteria for Diagnosing MS (Questions 1a and 1b)

The recently proposed McDonald criteria for diagnosing MS are well supported by two types of evidence. First, two studies show that between 73 and 94 percent of patients presenting with clinically isolated syndrome (CIS) who go on to develop clinically definite MS (CDMS) over 1-4 years of follow up could be diagnosed with MS according to the McDonald criteria. Furthermore, the specificity of these criteria is reasonably high, ranging from 83 to 87 percent. Second, many studies support the magnetic resonance imaging (MRI) component of the McDonald criteria, by showing a strong and consistent association between the number of T2 lesions on MRI and the subsequent development of CDMS among patients with CIS or optic neuritis. Thus the McDonald criteria appear to have substantial evidence for validity and offer the obvious potential advantage of resulting in an earlier diagnosis of MS than the Poser criteria permit.

The McDonald criteria have been criticized for their complexity in comparison with previous criteria; however, we found data that demonstrate that the McDonald criteria yield a good overall diagnostic reliability, at least as good as the previous Poser criteria. However, widespread adoption of the new criteria could result in deterioration of this reliability. Barkhof et al. (1997)[39] demonstrated that among neurologists inter-rater reliability of MRI diagnosis significantly improves with increased level of training. Non-neurologists are unlikely to be able to achieve the same level of MRI agreement and are therefore unlikely to be able to maintain this level of agreement with the McDonald criteria as a whole. Further research on the inter-rater reliability of these criteria in broader clinical settings would be helpful to determine the quality of MS diagnosis.

While these data may be sufficient to secure a place in clinical practice for the McDonald criteria, certain difficulties arise in applying these criteria retrospectively from medical record review for the process of determining disability. At the present time most patients have not been diagnosed according to the specific application of the McDonald criteria. Therefore, they may have medical records that do not clearly delineate the nature and timing of their specific MRI changes in a manner that conforms to the McDonald criteria.

Predictors of Physical and Mental Impairments at 12 Months (Question 2)

The ability to predict future course of MS has been an active area of MS research; however, most studies examining disease course do so over quite long time periods of 5 to 20 years. We found a paucity of data describing changes in neurological or other impairments over 9-24 months, which we used to approximate the 12-month time horizon dictated by statutory requirements. Clinical characteristics have been the best studied, with four reports providing evidence for this review. While clinical features do not individually provide reliable guidance on prognosis, multivariate predictive models based on relatively easy-to-obtain features may have better performance. However, the reliability and validity of these predictive models has not been evaluated and thus their value for predicting disability has yet to be determined.

In contrast to their value in predicting development of CDMS among patient with CIS, imaging studies do not appear to provide especially useful prognostic data among patients with MS. The absence of lesions on sequential MRI studies is associated with a lower probability of an exacerbation in the ensuing month, and long-term prediction of health outcomes needed in the context of disability assessments has not been shown to be possible. Somewhat more promising strategies for predicting outcome of MS patients is the use of laboratory markers, such as apolipoprotein E (APOE) $\in 4$ allele, interleukin-2 (IL-2) levels, or intrathecal immunoglobulin-M (IgM) synthesis, although the current level of evidence is best considered preliminary. These reports may provide the rationale for further validation studies, but are not standard practice and their practical impact is thus limited.

A single study of quality-of-life measures as predictors of long-term outcome was suggestive, especially considering the persistence of the association after adjusting for clinical characteristics. In addition to the uncertain generalizability of these results, such measures could have substantial reliability problems in the context of disability assessment.

Notably, no study was identified that examined the relationship between various factors and subsequent mental impairment.

Disease-modifying Therapies and Long-term Improvement (Question 3a)

Most of the data presented suggest that few patients improve on therapy. Those few who do improve generally do so only in the range of 1.0 point on the Expanded Disability Status Scale (EDSS). We found no data regarding improvement in work ability and no data that would correlate a 1.0-point improvement in EDSS with improvement in work ability. The significance of a 1.0-point EDSS improvement varies depending on baseline EDSS score (because the scale is non-linear), but the improvement data available are not generally stratified according to baseline EDSS score. With regard to work ability, the significance of the available data on clinical improvement is unclear. We found no data that quantified individual patient improvement with regard to cognitive function or quality-of-life measures.

In considerations regarding the determination of disability, the ability of a therapy to reduce mean exacerbation rates is of unclear significance. We have considered this issue out of concern that despite any given level of physical dysfunction, one might consider that an individual with frequent relapses may have impaired job performance solely on the basis of exacerbations. The

data presented in Table 6 (see Chapter 3) document that with any of the current therapies, mean reductions in relapse rates are generally less than one relapse per year.

The data examined in this evidence review do not support the conclusion that the current therapies are likely to result in substantial improvement in a significant proportion of patients with MS. This finding is consistent with expert opinion and demonstrated by the inherent design of current clinical trials, that is, the use of lack of decline in EDSS scores as the primary outcome measure. The present state of therapy is generally regarded as allowing for modest reduction in progression of MS – particularly in the relapsing-remitting patient population – but is not generally expected to result in significant long-term improvement. The rare exception is most likely in patients with relapsing disease who are progressing rapidly and undergo aggressive immunosuppressive therapy.

In general, the studies reviewed were not designed to answer the question we have asked. Indeed, individual patient improvement is not a common expectation of these trials. The authors believe that, despite the relative lack of data, the conclusions from the data examined do reflect the state of the current therapies. We believe that the data available document that individual patient improvement is an uncommon result of the current therapies. Further studies of currently available therapies would be unlikely to yield different conclusions; however, the recent trend of combining treatments in MS could yield different results. Combinations of currently available therapies and new therapies now under investigation may result in greater potential for individual patient improvement in neurological status.

Symptom Management and Improvement (Question 3b)

Treatment aimed at alleviation of symptomatic manifestations of MS, rather than the underlying disease, could have an important role in maximizing functioning among people with MS. Among the six areas we investigated, the degree of impairments and the effectiveness of the treatments varied. We review the conclusions and discuss the limitations and implications for further research by sub-topic below.

Spasticity. Although drugs such as baclofen, diazepam, dantrolene, and tizanidine are often used to reduce spasticity in MS, the research evidence for a beneficial therapeutic effect is inconsistent. This may be due, in part, to measurement issues. Spasticity is a difficult parameter to measure; too much muscle tone interferes with function due to spams and rigidity (resistance to movement); too little muscle tone can also interfere with function due to weakness. In some patients, a certain degree of elevated muscle tone in certain muscle groups can be desirable.

We had additional difficulty in estimating the clinical relevance of improvements that were reported, even when those changes were statistically significant. Many studies that dichotomized patients into “improved” versus “unimproved” failed to provide a definition or threshold of what changes represented “improvement.” Nonetheless, the relatively high baseline EDSS scores of patients enrolled in spasticity trials and unimpressive results of treatment suggest that anti-spasticity treatment is unlikely to have a clinically important impact on patients’ functional status, and is, thus, unlikely to impact disability determination per se. Furthermore, all of these drugs are limited by poor tolerability at therapeutic doses. Our findings were consistent with another recent systematic review.[204] Better measurement tools may be required in order to confirm the clinical impression that widely used anti-spasticity drugs such as baclofen, tizanidine, and dantrolene are more effective than placebo. Given current measurement

techniques, it is not surprising that active-treatment comparison studies fail to show clinically important differences among these drugs.

Rehabilitation. Physiotherapy interventions failed to influence impairments as measured by EDSS. These interventions were, however, associated with measurable changes in functional status. Improvements in health (handicap) were observed in the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) and several other measures. It is interesting that the historically first randomized controlled trial (RCT) of rehabilitation was not designed to assess the effectiveness of the intervention, but to evaluate whether less costly outpatient rehabilitation was as effective as inpatient rehabilitation.[139] Only more recently have trials been conducted that were designed to assess the value of rehabilitation compared to controls. Except for one study of supervised exercise,[143] the interventions employed in these studies were multifaceted, and it is difficult to attribute beneficial effects to particular components of the interventions. However, three other trials focused on non-physiotherapy interventions, which may be part of a rehabilitation program.[141,146,147] Two of these studies found changes in health measures (SF-36) not unlike those seen in physiotherapy-based rehabilitation interventions; however, these studies did not include measures of impairments or function.

Depression. Depression treatments, including psychotherapy, behavioral therapy, and certain drug therapies, can lead to measurable improvements in mood. There are fewer data linking treatment of depression to improvements in other symptoms (such as fatigue or cognitive impairments) or other outcomes (such as functional status or quality of life). The changes demonstrated in instruments designed to measure depression were not small but, still, the link to improved functional status and, further, to ability to work was not demonstrated in these studies per se. To do so would require extrapolation from studies of treatment of depression in non-MS populations.

Fatigue. Amantadine appears to have some ability to alleviate fatigue in MS, as demonstrated in statistically significant differences in some outcomes in several trials; however, the clinical significance of these effects is likely small. Pemoline has been less often studied and shows results suggesting some effect. There is little support for the efficacy of 4-aminopyridine. Modafinil has shown promising results in phase-II trials,[205] but has not yet been evaluated in a double-blind RCT. Measurement of fatigue is limited by a definition that spans several domains, leading to difficulty with validation. Further research on new pharmacological therapies (such as modafinil) and development of additional data on the validity of instruments for fatigue measurement and their sensitivity to change would be helpful directions for future research.

Voiding dysfunction. Desmopressin was highly effective at reducing urine volume and also consistently effective at reducing urinary frequency. This was demonstrated to translate into improvements in uninterrupted sleep hours and in fewer episodes of incontinence. Physical treatments, including both pelvic floor rehabilitation and use of a handheld vibrator during micturition, were also shown to reduce urinary symptoms compared with control. Only studies of pelvic floor rehabilitation measured impact on symptom-related handicap. These studies showed clear improvements in symptoms, but provided less clear data on how improvements in urinary symptoms impact other areas of health, and no data on how these symptomatic improvements might impact work ability.

Many interventions commonly used for urinary disorders in MS have not been studied in randomized controlled trials of MS patients. Commonly used interventions for which no RCTs have been performed among MS patients include anticholinergic and antimuscarinic drugs,

behavior modification, and intermittent or indwelling urinary catheterization. Data supporting their use comes from trials in other populations or from case reports/series in MS.

Cognitive dysfunction. None of the treatments studied has had a consistent measurable effect on cognitive performance in MS; however, the question has been little studied and indirectly studied, in the sense that most data on cognitive effects are inferred from studies aimed at treatment of fatigue or depression. One study suggested that fatigue symptoms do not correlate with cognitive impairment, although they do correlate with symptoms of depression.[159] Future studies would benefit from more precise delineation of study population based on screening for cognitive performance deficits within a relatively narrow and defined range; this would likely improve the chances of finding a treatment effect and also make clearer the population for whom the results would be applicable.

Association of Clinical Findings with Work Ability (Question 4)

Findings and limitations. There is a significant gap between what is included in the literature and the research evidence using objective measures for determining ability to work. Although objective physical and cognitive measures have been developed, their application in the occupational literature is sparse. Furthermore, assessment of how symptoms such as pain and fatigue impact work ability was essentially absent.

In epidemiologic research we draw conclusions from the body of existing work and never from a single study. There are criteria that aid in the judgment of causality called the Bradford-Hill Criteria,[206] which include strength of association, consistency of findings, temporality, dose-response relationship, biological plausibility, coherence, and specificity. After applying several of these criteria to the pool of information in this review we conclude that the research findings presented here are insufficient to demonstrate that a causal relationship between specific physical and/or cognitive measures and work ability has been established. The reported findings did display some consistency across studies. For example, individuals who had higher EDSS levels or low cognitive function were more likely to report not working. However, the strength of association across these studies was not clearly demonstrated, as most studies reported frequencies or crude estimates of association. Several studies consisted of small sample sizes, which hindered researchers from calculating risk estimates that were adjusted for potential biases such as age, education, level of employer assistance, job type, and desire to work. In addition, most studies considered only physical function or cognitive function, when both can hinder employment. A dose-response relationship of selected functional measures and degree of work capacity was not established. Because the majority of studies were cross-sectional, a temporal relationship between impaired function and inability to work was not established. Impaired function may not have occurred until after the study participants had ceased employment.

Although the bulk of these studies are descriptive in nature, they are useful for generating hypotheses for future studies to examine the causal relationship between impaired function and work ability. Some patterns that are noteworthy and should be considered when designing future studies to examine the risk of inability to work related to impaired function and adverse symptoms are as follows:

- The study outcome of work ability that extended beyond the definition of work status was informative for determining possible vocational rehabilitation potential for moderately to severely disabled individuals.

- As EDSS level increased, the frequency of reporting "not working" also increased. This same pattern was observed for the Hyllested criteria. However, there was considerable overlap between ability to work and EDSS level. Degree of disability or impaired physical function did not solely determine work ability.
- Level of cognitive impairment resulting in work inability was not adequately determined; however, the combination of both physical and cognitive measures proved necessary when assessing ability to work.
- Use of mobility aids and disease subtype as proxy measures for function provided very little information that was useful. Extrapolation of these definitions has the potential to lead to various interpretations, resulting in limited application of findings.
- Individuals with jobs that required less physical exertion were more likely to report remaining employed. These findings supported studies that measured both physical and cognitive function directly.
- The impact of fatigue on work ability was captured only through self-report. Direct measures of fatigue did not appear in the included studies.

In conclusion to the findings presented here it is important to discuss a significant limitation of observational research as it relates to determining if an individual with MS is able to work. Population-based epidemiologic research is useful for determining patterns, trends, and causal relationships between exposures and disease outcomes among groups of individuals, but in prior studies[207,208] researchers have demonstrated that risk factors or combinations of risk factors included in a statistical model serve as poor screening tools at the individual level. In the case of MS, future epidemiologic studies may indicate that certain physical or cognitive function tests are strongly associated with inability to work; however, extrapolation of these findings for the purpose of predicting work ability at the individual is not possible.

Future research. Future research about work ability among individuals with MS can shed a great deal of light on factors that foster or hinder employment. Work ability involves numerous medical and non-medical factors that have been discussed in great detail. In light of the gaps in the current literature, it would be advantageous to design future research endeavors to simultaneously address the following domains:

1) *Objective clinical data:* Collect data on clinical measures, such as disease subtype, that the Social Security Administration (SSA) typically uses when determining disability among individuals with MS. Data collection should be tailored to gather information from medical records that SSA deems relevant to its process.
2) *Physical/cognitive/symptom measures:* Objective measures of physical and cognitive function, as well as symptoms such as fatigue and pain. Consider the tools that have been well established and tested for measuring these types of impairments. As previously noted, the use of well-established tools in the occupational literature has been sparse with regard to MS.
3) *Work ability measures:* The measurement of work ability should be extended beyond the definition of work status to include examination of skill level, education level, career interests, willingness to work, and vocational rehabilitation potential.
4) *Occupational requirements/employer accommodations:* Assess job responsibilities and employer's willingness to provide accommodations in tandem with work ability measures. Current occupational requirements may not match with current level of function.
5) *Demographics:* Age, sex, education level, marital status.

6) *Family responsibilities/support:* Family demographics, income, responsibilities, number of children, and number of elderly parents who need care.
7) *Subjective reports from individuals with MS:* Qualitative information about hindrances and enhancers of work, including characteristics specific to the job or workplace and symptoms related to MS.
8) *Subjective reports from employers:* Qualitative information about how employers are able to provide accommodations and support for workers who have significant and/or intermittent fatigue, pain, and other symptoms related to MS. Gather information about how employers accommodate workers who also have physical and/or cognitive limitations, as well as information about conditions or situations where they cannot provide accommodations.

We suggest that a series of case-control studies be conducted, as well as a prospective cohort. For both these study designs, we suggest that resources already available through MS research centers across the country be used. A recent report by the Institute of Medicine[209] describes certain limitations of research based in MS centers, but indicates that multisite research of this sort is valuable for conducting epidemiologic studies requiring a large number of patients with MS. Conducting a series of studies at several centers in the US could provide consistent evidence across numerous populations and geographic regions. Furthermore, data needed about employment history and disease progression may already be collected for established patients enrolled in ongoing studies. It is recommended that SSA collaborate with the National Multiple Sclerosis Society when selecting sites for this research.

Although it would be ideal to conduct a prospective cohort study for the purpose of establishing a temporal relationship between impaired function and work inability, this could take considerable time and money. We recommend initially a series of case-control studies where cases (defined as individuals with MS who are no longer employed) and controls (defined as individuals with MS who are still employed) are compared on the numerous domains described above. This should provide SSA with more detailed information about the types of clinical measures it currently deems relevant for determining work ability. Sample size was an issue in almost every study included in the review. Sample sizes should be large enough to detect true differences between groups, especially when considering cognitive function. Furthermore, the sample size should be large enough so that subtype of disease can be appropriately considered through stratified analyses. The pattern of disease progression varies between disease subtypes in ways that could influence employment. For example, patients with relapsing-remitting MS may not be able to remain steadily employed because of the erratic and unpredictable nature of disease exacerbations, whereas individuals with primary progressive MS may have a more predictable disease course that does not intermittently interfere with work. Although there is significant overlap of symptoms between the current disease subtypes, ability to work may vary considerably between them.

The case-control studies should be advantageous for examining the timing or sequence of clinical information and physical and cognitive function testing prior to cessation of employment. Demographic information would most likely be available as well. However, information surrounding employment issues, triggers for leaving work, obstacles or enhancers to work, and employers' willingness to help may not be available. In order to capture this information, especially around the time that an individual with MS decides to leave work, we recommend that researchers conduct a prospective cohort study. Incident cases of MS must be captured and followed over time so that changes in physical and cognitive function can be

examined in relation to ability to work. Ideally, incident or fairly recent cases where the individual is still employed should be captured for follow up. As previously indicated, it would be ideal for researchers to build on prospective studies that are already ongoing. Information needed for this study could be added to what is already being collected for other studies.

The qualitative data collected through focus groups, personal interviews, and surveys have proven invaluable for guiding quantitative analyses. Information gathered from individuals with MS, as well as their employers, could provide a great deal of information about the types of accommodations that are useful and effective. Furthermore, companies may struggle with providing accommodations, especially with an individual who has frequent relapses.

Several study limitations have been highlighted in this review, as well as patterns of findings, which should be considered when developing future research. Future studies that consider the multiple factors influencing work can lead to generating unbiased risk estimates of inability to work among individuals with MS. In the development phase of these studies, it is imperative that SSA be involved in determining the types of data to be collected. Data collection should reflect the information that SSA deems important when making decisions about ability to work.

Findings in the context of other literature on work and MS. Several of the studies included in this review reported findings or trends about their study populations that reflect what is already known or established in the literature about issues surrounding employment independent of MS and vice-versa.

The onset of MS occurs between ages 15 to 50 years for approximately 90 percent of cases.[210] Thus, MS strikes individuals during peak years of education, training, and employment. Labor market analyses by the Bureau of Labor Statistics[211] reported that, in general, higher levels of education enhance labor force participation, and severely disabled individuals are more likely to participate in the labor force if they have a college degree (57 percent) compared to disabled individuals with less than 4 years of high school (17.3 percent), high school completion (31.2 percent), and some college (39.1 percent).[211]

The incidence of disease is twice as high among women as among men.[195] MS impacts women not only during peak years of employment, but also during peak reproductive and childbearing years. Attachment to the workforce among first-time pregnant women in the US is influenced by several factors including age, education, years of work experience, and whether or not they were employed and established in their careers prior to the onset of pregnancy.[212] The domestic responsibilities that follow pregnancy influence employment as well: compared to unmarried women without children, both married mothers and single mothers commit far fewer hours to the workforce (although the differences have declined significantly over the past two decades).[213] Some of the studies included here concurred with these findings in that women reported leaving work for reasons unrelated to MS, but related to domestic responsibilities.[191] It can be especially challenging to distinguish between the impact of MS and the responsibilities of childrearing among women when examining ability to work. Some studies recognized these sex differences by controlling for them in their analyses.[183,186,187]

Symptoms associated with MS vary between individuals, but can include fatigue, ataxia, dementia, optic neuritis, bladder urgency and incontinence, spasticity, pain, and sexual dysfunction.[195] As reported above, fatigue was the most common reason individuals with MS reported ceasing employment;[177] however, fatigue, like pain, is very subjective and difficult to measure (see discussions of Question 3b in this and previous chapters).

The importance of employer involvement in providing accommodations for disabled individuals was nationally endorsed in 1990 with the enactment of the Americans with

Disabilities Act (ADA). In an earlier study by Mitchell (1981)[214] two-thirds of male postal workers with MS received work accommodations with respect to their MS related work capacity, which enabled them to remain at work. With the ADA in place for more than a decade, and MS representing the third most common neurological diagnosis that SSA receives,[1] the paucity of information in the literature about how employers have enabled individuals with MS to remain at work exists is unfortunate.

Environmental Factors and Work Ability (Question 5)

Current clinical wisdom about thermal sensitivity in some MS patients is based not on large controlled research studies but rather on a combination of many decades of clinical observations, case reports, small trials of thermal challenge outcomes, and reports of beneficial therapeutic effects of body cooling. The present report, while not directly addressing the question, provides no basis for rejecting such clinical observations that excessive heat can have an adverse temporary effect on the well-being and symptoms of some MS patients.

With regard to work impairment, limitation, or disability related to temperature conditions, we found remarkably little research that met our inclusion criteria. This should probably not be surprising. The difficulties of conducting population-based research on work capacity in patients with MS are reflected in the discussion of Question 4. Given this reality, researching temperature as an independent determinant of functional capacity would be particularly challenging.

There remain important questions about what proportion of MS patient populations may be thermo-sensitive, to what degree, and why?[197,200] As to temperature sensitivity significant enough to impede work, this report found only one includable report.[182] This study has significant limitations in its generalizabililty to a Social Security Disability Insurance (SSDI) applicant pool due to a number of issues, including the fact that the assessment of thermal sensitivity was completely subjective. The low percentage of respondents citing thermal factors in this study suggests that exposure to heat is not among major perceived critical job demands.

Of interest, there is little or no report of thermal factors in other studies that might have identified perceptions of workplace temperature[193] or self-reported thermal sensitivity[177,185,192] as variables that impede work or affect employment status.

It is possible that most MS research has focused at a more primary symptom level (e.g., affective lability, numbness, speech, fatigue, cognition, ambulation, vision, incontinence) without addressing more subtle factors, such as temperature, that may exacerbate symptoms. Forced-choice questionnaires, for example, may not include an option to report thermal sensitivity.[179]

We conclude that answers to Question 5 remain mostly unknown. The evidence provides no basis for generalizations such as maximum appropriate working temperature levels unique to MS patient populations. The one included report confirmed that some MS patients perceive heat to impede their work capacity. It is not likely that medical data in SSDI application files in the current era will include objective diagnostic test results identifying MS patients who respond adversely to heat challenges.[215] However, subjective patient reports may describe such associations with or without clinician comment or correlation with objective clinical status measures. Although not necessarily founded on randomized controlled trial data, current clinical impression seems to hold that ambient and/or exercise-induced body temperature effects may

bear a relationship to MS symptom status in some patients, perhaps more so than is thought to be the case for chronic disease states in general.

Knowledge Gaps and Future Research Recommendations

This report has identified several gaps in current knowledge that can direct future research. Regarding diagnosis of MS, the available studies evaluating the validity and reliability of the recent McDonald criteria,[5] though few in number, are strong and consistent. The evidence reviewed suggests that diagnosis of MS using MRI data as implemented in the McDonald criteria has good validity compared with ultimate clinical diagnosis; further research is needed on the prognosis of patients diagnosed with MS using McDonald criteria, especially with regard to the ability of clinical or radiographic features to predict clinical outcomes.

Regarding prognostic studies, most studies report prognosis over long periods of time, over which MS shows inexorable progression. Shorter-term studies demonstrate a high degree of variability, and few factors seem to predict near-term prognosis. Studies of prognosis are needed that focus on the early disease course (an inception cohort) defined by McDonald criteria; such studies may be more fruitful at identifying prognostic factors than previous research has been. Data of this sort may be most efficiently gathered in the course of disease-modifying treatment trials, which are also a high priority in this population.

Regarding treatment issues, while differences in relapse rates and EDSS scores between control groups and groups receiving disease-modifying agents have been modest, reductions in disease activity as measured by MRI have been marked; the long-term significance of this reduction is not yet clear. Whether the failure to show differences in clinical outcomes is a limitation of the EDSS, the efficacy of the experimental agents, or the follow-up time is uncertain. Further treatment studies are needed that (1) target earlier disease (as diagnosed by McDonald criteria) and (2) are large enough and long enough to correlate MRI response with clinical response. Furthermore, while disease-modifying drug treatment trials have focused on physical function outcomes, this choice of outcome measure may preclude evaluating whether these treatments prevent or slow the development of cortical atrophy, which may correlate better with disability in MS.

Regarding symptomatic treatment issues, of the six symptomatic areas we explored, several were well covered. Spasticity drug treatments have been well studied, although the clinical relevance of the major outcome measure used in these studies, the Ashworth Scale, has been questioned. Further research on spasticity should be directed at evaluating functional status outcomes rather than muscle tone outcomes; and while drug treatments may be important, greater attention should be directed toward physical therapy, rehabilitation, and behavioral approaches instead of, or in addition to, drug treatments.

Treatment of fatigue has also focused on drug treatments, which have been largely unsuccessful. A new drug agent, modafinil, is currently under study, and may prove more useful; however, further research in non-drug approaches instead of, or in addition to, drug treatment may be necessary.

Mental and psychological functioning in MS has rarely been the target in intervention trials, although mood and cognitive disorders have been shown to be prevalent in MS. Further attention is warranted toward measurement of these impairments with the goal of developing

outcome measures for disease-modifying drug treatment trials or symptom-directed intervention trials.

The major clinical interventions in urinary management in MS were little studied in MS patients specifically; it is unclear whether further research on groups of subjects with MS would be fruitful.

Regarding ability to work, this report highlights significant evidence and information gaps concerning:

- patterns of MS patient reports regarding functional limitations;
- information commonly collected in medical encounters with MS patients (and therefore available to SSA);
- knowledge about the impact on performance of specific work tasks of commonly objectified parameters such as coordination, strength, and vision, and especially of factors such as fatigue or cognitive dysfunction, which are either difficult to measure or are less commonly assessed in detail; and
- effective research methods for categorizing job or task demands in such a way as to isolate those demands that are likely to be "critical" for an SSDI applicant with MS.

In the context of these gaps, it may be productive to pursue research approaches that simultaneously address four domains:

- subjective reports (this domain is not sufficient alone for SSDI determination purposes);
- objective clinical data (ideally of the sort commonly encountered in medical records);
- in-depth objective measures (which may be available and not widely applied clinically, but which may be used with subsets of subjects to explore correlation with other domains); and
- work status measures (ideally longitudinal, with stratifications based on work demands).

Such an approach may apply to thermal sensitivity as well, with some additional specification and focus. Parallel assessment of concomitant ambient temperature, physical exertion, and core body temperature would address key relevant physiological exposure factors. Outcome measures could include the domains outlined above, for example:

- self-perceived well-being and level of symptoms such as fatigue;
- clinical parameters such as walking speed or muscle strength;
- in-depth measures such as potentially associated biomarkers or physiological parameters;[199,200] and
- work status measures, including absenteeism and disability benefits use.

Obviously, considerable caution would be required for subject safety related to heat exposure.[216,217] Such a research approach would be relatively complex and expensive, but might provide relevant information in the arenas of basic science and clinical care, and to a broad range of agencies, employers, and insurers dealing with MS work capacity issues.

Generating research results of practical relevance to SSA would, in some ways, be an even more demanding goal. The range of potential job situations in question for SSDI determinations always has the potential to extend beyond the claimant's own or previous occupation to a wide range of substantial gainful employment possibilities.[218] Heat exposure may well be an MS-related critical job demand in the context of various degrees of outdoor physical labor in warm climates. However, it seems likely that less physically demanding work in temperature-controlled job environments would frequently be the relevant job capacity circumstance by which SSDI applications were ultimately determined. Therefore, it may be necessary to use a narrower range of exposure and outcome variables in order to address the actual questions that might arise in the SSDI process. Such restrictions may limit a study's power to demonstrate

associations or effects. The likely value to SSA of such an effort may well be influenced by an awareness of the frequency of and the particular circumstances surrounding SSDI determination situations in which thermal sensitivity is a critical determinant of the process outcome. Historical SSDI information may shed light on those particular permutations of ambient workplace temperature and physical demands that have commonly represented a critical or significant question in SSDI determinations.