Potential Chromosome 12 Locus for Late-Onset Familial Alzheimer Disease

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Letters

Defining and Measuring Quality of Life in Medicine

To the Editor.—Drs Leplége and Hunt[1] assert that variability across cultures, between patients, and in the same patient over time makes efforts to define the term *quality of life* impossible. It is an "idiosyncratic mystery." They conclude that physicians and health economists should avoid quality of life assessment. At the same time, the authors assert that quality of life is paramount to patients and is, indeed, the only concern of the patient who seeks medical care. The unwelcome conclusion is that outcomes—whether patients feel better and are able to do more, whether they are spared subsequent treatments, and whether they are glad they sought medical care—are not a part of medicine.

This argument, however, rests on a faulty assumption. Variability among patient appraisal of quality of life is limited. No one thinks severe abdominal pain is better than a runny nose, as Fanshel and Bush[2] long ago pointed out (even if it is difficult, as they recognized, to find a measurement unit that expresses their relative quality-of-life impact). Even cultural variation has limits. When asked about their ability to carry out common tasks of daily living, the responses of !Kung and Herero elders of southwest Africa (seminomadic pastoralists) were best understood in terms of a physical function component highly correlated with age.[3] More generally, utilities elicited for health states are highly correlated across populations and across sociodemographic groups.[4] If health state utilities do vary according to patient health status (as demonstrated for dialysis patients[5] but not, however, for all patient groups), this variability only shows that other distinct features of patient experience must be considered by clinicians when recommending treatments or assessing outcomes. These include family support systems, willingness to adopt prosthetic technologies, and patient attachment to life.

Leplége and Hunt have exaggerated the idiosyncratic nature of health-related quality of life (HRQL) by confounding it with quality of life more generally. This distinction is critical: HRQL measures are likely to be more highly correlated with health status and more sensitive to changes in health than general quality-of-life measures. When the authors suggest that quality of life be viewed as "the best possible physical and emotional state compatible with [a patient's] medical condition," they are talking about HRQL, which is already well assessed by a variety of measurement tools. When they complain that such measures of health status do not capture other components of patient quality of life, such as the capacity to love or have "a positive approach to everyday events," they are right, but the measures also were never intended to do so.

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To the Editor.—Drs Leplége and Hunt[1] provide an incomplete view of the current state of the science of HRQL measurement. We disagree with their pessimism about the value of aggregated and normative outcome measures. Health outcomes researchers must specify the conceptual model underlying an instrument; the patients' perspective is critical in the development of HRQL measures. We agree that patients are the main source for information about the content and importance of domains to ensure that a quality-of-life measure adequately reflects the impact of disease on functioning in everyday life and well-being. Most current instruments start with eliciting concerns from patients (by qualitative methods or focus groups) to determine the relevant domains.

Problems with confusing and unclear terminology have continued in HRQL research. The use of "subjective health status" rather than "quality of life" will not resolve the problems the authors have raised. We use HRQL when addressing quality-of-life outcomes that can be affected directly by health care interventions, a stance consistent with Wilson and Cleary,[2] reserving quality of life for the global appraisal of life quality. Patient outcomes describe the full range of measures used in health evaluation, including clinical measures, symptoms, functioning, and well-being.

Cultural differences present another challenge to HRQL assessment. Studies have demonstrated that important domains, such as physical, social, and psychological well-being, are consistent across cultures. It is the expression of these domains, including the range of activities and behaviors, that varies within and between cultures and countries. The challenge is to design instruments to assess HRQL in culturally meaningful ways and apply scientifically based methods for linguistic and cultural validation.

Patients' adaptation to and acceptance of their disease state can lead to the apparent discordant finding that normative health status measures demonstrate severe functional limitations, while subjective ratings reflect patients' satisfaction with the quality of their life. Both perspectives are important in evaluating the impact of health interventions. Idiographic measures are useful for understanding the characteristics that drive individuals' assessments of their quality of life. Standardized, normative measures are useful for making comparisons of health care interventions and different populations. Applications of techniques, such as 3-mode factor analysis,[3] that combine the normative and idiographic approaches can be used to further understand responses to assessment instruments.

Methodological advances in health outcomes assessment over the past 30 years have facilitated the introduction of patient outcomes in clinical trials, the monitoring of the health

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populations exposed to different systems of health care delivery, and individual patient care. No single approach to measuring patient outcomes will likely meet the needs of all clinical and research applications. Multiple, reliable, and valid measures are needed to take into account the unique perspectives of patients and the perspectives of physicians and the health care system, with all the attendant conceptual and methodological challenges. We think that the application of patient-centered health outcomes to medicine represents an important advance in the humanistic delivery of health care.

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1. Leplége A, Hunt S. The problem of quality of life in medicine. *JAMA.* 1997;278:47-50.
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To the Editor.—Drs Leplége and Hunt[1] raise important concerns about quality-of-life measurement in medicine. However, we take issue with 3 critical points. First, quality-of-life methodology does not always "ignore the relative meaning and importance given to such tasks and roles by the individual." Some questionnaires are beginning to be used, such as the Schedule for the Evaluation of Individual Quality of Life[2] or the Functional Assessment of Cancer Therapy,[3] that include for each domain a patient-assigned score related to overall quality of life (multiattribute method of preference assessment). In such instances, patients can weigh the importance of any domain referred to their own life, and individual judgments can be modeled mathematically. This approach, although time intensive, aims to improve quality-of-life methodology and attempts to alleviate problems related to the generalizability of standard instruments.

Second, Leplége and Hunt write that "too often, the patients are asked to complete questionnaires that do not reflect their concerns." But for almost all quality-of-life questionnaires, item generation is performed with patients believed to have particular insight into the condition under study and with patient focus group discussions.[4] Moreover, many instruments or modules are constructed, with the same method, for specific diseases[5] to increase sensitivity of measurement.

Third, and most important, we are attracted to the "existential approach" and its particular attention to the individual, but we believe in the usefulness of a scientific method to measure quality of life. Usually the objective of a study is not to find the greatest good for a single person but the greatest good for a population, moving from an individual perspective to a societal one. Even for quality-of-life measurement, only large clinical studies, designed and conducted with rigorous statistical standards, allow a hypothesis to be tested and, thus, offer useful results. We believe that this is possible for quality-of-life assessment, until new scientific approaches are validated, by formulating standardized questions and analyzing answers with standardized modalities. For this purpose, psychometric properties must be evaluated to demonstrate the reproducibility of a method. Nevertheless, universal results can be individualized and personalized.

We believe in evaluating the patient's perspective of his or her own health status. It represents a valid attempt to get over the supremacy of "objective" to look more attentively for the needs of any person. The quality-of-life method is useful in implementing the patient's point of view into clinical practice and decision processes. Therefore, future efforts should address improving quality-of-life definition and methodology and diffusing it into clinical settings.

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To the Editor.—Drs Leplége and Hunt[1] are correct to question the current use of quality-of-life assessment. In practice, quality-of-life questionnaires are all, in one form or another, complaint checklists, and when quality of life is measured in this way, the concept becomes equivalent to absence of health complaint. Is quality of life really just the absence of complaint? As in Aesop's fable of the fox and the sour grapes, people change their goals when they find those goals to be unattainable. The gap between desire and attainment can be reduced as much by a diminution of desire as it can be by increased functional attainment, although whether it is good to attenuate desire is a value judgment. Contrary to what Leplége and Hunt say, quality-of-life scales do not measure functional ability, they measure willingness to complain about perceived functional disability.

Quality of life is a phrase, nothing more, but whether the phrase is used by lay people or academics, it carries existential assumptions about what is good in life. What is good in life depends on the meaning of life. Quality of life is actually an evaluation of life based on the particular value system that a person has about the meaning of life.[2] For the busy physician, that value system may be absence of health complaint, but for the average person, quality of life may mean much more.

Problems with quality of life are not only conceptual. The philosophy of medical measurement is that measurement instruments remain constant irrespective of who is using them: a thermometer remains the same whoever's mouth it is placed in. Questionnaires do not obey this same principle of invariance. More than 50 years ago, psychologists measuring intelligence realized that tests are culturally biased and that the same test is interpreted differently by people from different cultures.[3,4] Very much the same happens with quality-of-life assessment. If a global scale of quality of life is used—ie, when patients are asked directly to evaluate their quality of life on a single scale—the meaning of the term *quality of life* will be interpreted differently by different respondents.[5] The same questionnaire is not an identical tool in the hands of different patients, even though it looks the same to the researcher. The conclusion to draw is not that quality-of-life measurement should be abandoned, but rather that the use of the concept needs to be placed more firmly in the context of alternative value systems and measurement theory.

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1. Leplége A, Hunt S. The problem of quality of life in medicine. *JAMA.* 1997;278:47-50.
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To the Editor.—Drs Leplége and Hunt[1] introduce and discuss some relevant issues related to the use and actual value of the term *quality of life* in medical research. The hub of their interesting paper is that there is confusion in the field, mainly resulting from the lack of valid and robust conceptualization of the very concept that it is intended to measure. In other words, the central point is that when using HRQL instruments, what we, at best, actually measure is the "objective" health status filtered by the patient's "subjective" perception of health, forcing the patient to deal with a model of health and illness that is the product of the medical point of view. Leplége and Hunt challenge the current approach, and, although acknowledging the positive effect of giving prominence to the patient experience and point of view, they suggest abandoning these misleading terms, favoring the use of "patient's subjective health status" and passing from the utilitarian to the existential approach.

Most of the article raises "hot" points that are frequently debated in the corridors of the several meetings addressing HRQL topics, but they are less frequently explicitly addressed in formal articles, with some exceptions.[2,3] Therefore, it is easy to agree with Leplége and Hunt regarding the fact that the current approach to define HRQL as a mere physical, psychological, and social measure of patients' self-perception of their current health[4,5] implies a too simple and naive conceptual model that might falsely reassure some but does not actually satisfy others.

The current dominant medical approach fails to take into account all the possible interconnections between medical, nonmedical, and individual factors that play a role in the complex relationships that exist between the potential determinants of health and HRQL. The underlying assumption is that medicine can largely affect the health of individuals; most of the reliable variability in health outcomes is because of the effectiveness (and quality) of care and the severity of illness. Nonmedical determinants are considered to play a minor role and are, therefore, treated as confounders. In this cost-conscious era when health care is delivered in the framework of "canalized" health programs to healthy individuals or to chronically ill patients, this assumption can and should be challenged.

I fully agree with Leplége and Hunt regarding the need to reconsider the approach and to abandon the terms we use currently, but it is still not clear how to operationally introduce what they call the "existentialist approach." The use of the existentialist approach can give us a way to understand the limitations and disadvantages of current methods, but how can we operationally introduce these challenging critiques in our everyday effort to assemble the best indicator of patient benefit in studies assessing the value of pharmacological and nonpharmacological intervention on patient health?

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In Reply.—In response to both the critical and sympathetic letter authors, our main concern is that there seems to be some discrepancy between the prevalent discourse of what quality-of-life and HRQL instruments are supposed to measure and what they actually do measure. In our technical jargon, we would say that there is a content validity issue (ie, most so-called quality-of-life instruments do not measure quality of life but health status instead). We think that such a situation should be dealt with seriously, since stating that the outcome of a given medical intervention is an improvement in the quality of life of the recipients may raise undue expectations among the patients, the medical community, the public, or the regulatory authorities. Therefore, we believe our responsibility is to address this problem publicly and call for a much needed debate.

All of these letters published in reply to our article contribute to such a debate. However, some of them are not immune to the terminological and conceptual confusion that we criticize. For example, Dr Albert quotes several studies that demonstrate that there exist commonalities across cultures in terms of physical function, values associated with health states, and health status. Unfortunately, this contradicts the main rationale for the development of this area, ie, we cannot assume quality-of-life improvement from an improvement in health status or physical function. Dr Frank and colleagues write that they use the term *health-related quality of life* "when addressing quality of life outcomes that can be affected directly by health care interventions." But since those instruments that are currently supposed to quantify HRQL have been conceptualized, developed, and published as health status questionnaires, it is difficult to believe that nothing other than a terminological change has occurred. Albert writes that our unwelcome conclusion is that "outcomes—whether patients feel better and are able to do more, whether they are spared subsequent treatments . . . are not part of medicine." Naturally, we believe that it is important to assess whether patients feel better or not, but we maintain that medicine has plenty of outcomes of its own.

The main challenge for any model nonclinical outcome assessment tool is to reflect the viewpoint of the patients. In this regard, Dr Murri and colleagues quote 2 of the few instruments that represent significant advances in the right direction. The letters by Dr Apolone and Dr Hyland illustrate 2 interesting proposals for the development of such an operational definition and the understanding of its limits. However, we still feel that further discussion is necessary before an operational definition or theory of what quality of life is, based on empirical data, can be agreed on.

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Chronic Fatigue Syndrome

To the Editor.—In his discussion about chronic fatigue syndrome (CFS), Dr Komaroff[1] states that, in addition to symptoms included in the case definition, many patients with CFS also frequently report anorexia, nausea, and dizziness. Counting these latter symptoms, which have also been found in adrenal insufficiency,[2] CFS shares 23 features with Addison dis-

ease,[3] including both the symptoms of the case definition for CFS and all the neuropsychological complaints that have led some people to claim that CFS is just a manifestation of an underlying depression. Considering that no medical condition except Addison disease shares more than 20 features with CFS, it is unclear why no study to my knowledge has been performed to determine whether the treatment for Addison disease, ie, hydrocortisone plus fludrocortisone acetate, could also benefit CFS patients. Fludrocortisone is likely to be of benefit based on a previous study in patients with CFS.[4]

Komaroff claims that CFS occurs in all ethnic and racial groups. African Americans, however, rarely seem to develop CFS.[3]

As Komaroff points out, depressed function of natural killer cells represents one of the most robust findings in CFS. In view of the fact that natural killer cell activity is directly associated with the circadian rhythm of cortisol,[5] it can be reasonably suggested that the depressed function of natural killer cells in CFS patients simply mirrors their hypocortisolism.[3] This explanation is in accord with the opinion that the chronic immune activation observed in CFS does not occur because of an infectious agent, but because of a mere lack of steroid restraint on the immune system.[3]

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To the Editor.—Although Dr Komaroff[1] concurred with the proffered diagnosis of CFS, I believe another possible cause was overlooked.

Ms H, the woman presented, had a history of recurrent episodes of sinusitis predating her current illness. That illness started with symptoms compatible with acute sinusitis: fever, chills, myalgias, and sore throat. Her prolonged course has been characterized by exhaustion, bodily pains, "swollen glands," sore throat, sleep disturbance, and headaches. Methylphenidate hydrochloride, 1 of her 3 medications, is taken daily to relieve nasal congestion.

Sinusitis can cause each of the above symptoms,[2,3] but the duration and degree of disability would, I suspect, make this diagnosis implausible to most internists. The education and training of internists is, however, quite scant on the subject of chronic sinusitis.[4] Clinical reviews exploring the systemic systems of chronic sinusitis are limited to recent reports in the otolaryngological literature.[5]

Gliklich and Metson[5] reviewed the health status of chronic sinusitis patients referred for otolaryngological care. Cases were compared with the US general population using data derived from the Medical Outcome Study Short-form 36-Item Health Survey. Those with chronic sinusitis were significantly more impaired in areas of bodily pain, general health, vitality, and social functioning. Compared with individuals with congestive heart failure, angina, chronic obstructive pulmonary disease, and back pain, those with chronic sinusitis were significantly more impaired in measures of bodily pain and social functioning. The above findings are more striking since the patients in the chronic sinusitis population of this study were an average of 20 years younger than those in the Medical Outcome Study.

Ms H's case may represent an unusual manifestation of a very common illness, an illness apparently capable of causing symptoms qualitatively similar to the ones she found so troubling: fatigue and bodily pain. Nasal examination and sinus computed tomography should, I feel, be included as part of her evaluation since treatment offers a reasonable hope of significant improvement.[6]

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6. Gliklich RE, Metson R. Effects of sinus surgery on quality of life. *Otolaryngol Head Neck Surg.* 1997;117:12-17.

To the Editor.—I was surprised that in the evaluation of a 56-year-old woman with chronic fatigue[1] and in the discussion of the differential diagnosis that followed, no consideration was given to B_{12} deficiency. Fatigue, memory loss, weakness, changes in mood, and visual loss have all been reported to be associated with B_{12} deficiency in the absence of anemia and macrocytosis.[2] B_{12} deficiency has also been reported to cause reversible white matter lesions on magnetic resonance imaging scan.[3] Thus, determination of a serum B_{12} level and, in borderline cases, serum methylmalonic acid and homocysteine levels[4] should be part of the routine evaluation of a patient with chronic fatigue. I would be interested to learn this patient's B_{12} level.

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1. Komaroff AL. A 56-year-old woman with chronic fatigue syndrome. *JAMA.* 1997; 278:1179-1185.
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In Reply.—Dr Baschetti correctly states that many of the symptoms of Addison disease overlap those of CFS. As I mentioned in the case discussion, formal studies of the hypothalamic-pituitary-adrenal axis in patients with CFS have suggested a central underproduction of corticotropin releasing hormone but have not found evidence of primary adrenal insufficiency.[1] Moreover, a randomized controlled trial of low-dose cortisol replacement therapy has been conducted by the National Institutes of Health. The unpublished study, reported at a scientific meeting,[2] found no benefit from replacement therapy.

Baschetti challenges the claim that CFS occurs in all ethnic and racial groups. I agree that, among patients seeking care for CFS, racial minority groups are underrepresented. However, a community-based epidemiologic study by our group found that black and Latino patients were not underrepresented,[3] a finding confirmed by a second community-based study being conducted by the Centers for Disease Control and Prevention.[4]

Dr Chester has long championed the plausible theory that chronic sinusitis could explain many of the symptoms of CFS. However, there is as yet no published study showing a higher frequency of chronic sinusitis in patients with CFS than in control subjects, nor is there a controlled study showing that the symptoms of CFS improve with treatment for chronic sinusitis.

Finally, I agree with Dr Devitt that vitamin B_{12} deficiency can produce central nervous system symptoms and signs with-

out producing the associated classic megaloblastic anemia. However, the 1 randomized, placebo-controlled trial of vitamin B_{12} replacement therapy in patients with CFS showed no benefit.[5] I do not know enough about the prevalence of "borderline" vitamin B_{12} deficiency—in patients with CFS or in the population at large—to warrant routinely obtaining the expensive laboratory testing suggested by Devitt.

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Potential Chromosome 12 Locus for Late-Onset Familial Alzheimer Disease

To the Editor.—In the article by Dr Pericak-Vance and colleagues,[1] data obtained from a genomic screen in families with late-onset Alzheimer disease (AD) suggest the existence of a potential genetic risk factor on chromosome 12. Parametric and nonparametric linkage analyses demonstrated the strongest association for *D12S373*, *D12S1057*, *D12S1042*, and *D12S390* in families that had at least 1 affected individual whose apolipoprotein E (*APOE*) genotype did not contain the ϵ4 allele (*APOE* ϵ4), suggesting that this region may harbor a new late-onset AD susceptibility gene with little or no dependence on *APOE* ϵ4.

In our studies in a large, multigenerational family with late-onset AD,[2] including a genomic screen, we have attempted to identify additional genetic factors contributing to familial AD. Preliminary 2-point linkage studies using an autosomal dominant and age-dependent penetrance model revealed a weak association in a 9-centimorgan (cM) region on chromosome 12 flanked by markers D12S391 and D12S373. The maximum 2-point lod scores were 0.5 and 0.7, respectively. In light of the findings of Pericak-Vance et al,[1] and given that our initial screen implicated a region approximately 30 cM from their maximum lod scores, we performed further analysis using markers D12S1057 and D12S1042. Our results show no detectable linkage with D12S1057 and D12S1042 (maximum 2-point lod scores of 0.006 and 0.1, respectively) suggesting either the existence of a risk factor located more telomeric to that which has been presented or a contributing genetic factor common only to families not linked to *APOE* ϵ4. Although our data reflect a single, large family with a predominant *APOE* ϵ4 effect on onset of AD, we believe that these findings may contribute to the characterization and assessment of potential genetic risk factors involved in the pathogenesis of AD. Our continuing efforts will include fine mapping and multipoint analysis of this and other isolated regions.

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In Reply.—The results of our complete genomic screen suggested the location of a potential new locus on chromosome 12 for late-onset AD. The chromosome 12 results were strongest in large, extended, multigenerational AD families (tier 1 in our article) that had little influence from the *APOE* ϵ4 allele (ie, 1 or more affected family members were *APOE*–X/X, where X is the *APOE* ϵ3 allele or *APOE* ϵ2 allele). While our pedigree structures are similar to, but not as extensive as, the family described by Dr Martin and colleagues, their family is different in that it is strongly influenced by the *APOE* ϵ4 allele, and virtually every affected individual has, or can be inferred to have, at least 1 *APOE* ϵ4 allele.[1] Thus, it is likely that the genetic effect on AD in their family is primarily from the *APOE* ϵ4 allele. Considering that the effect in our tier 1 families was independent of the *APOE* ϵ4 allele, the results described by Martin and colleagues are in accord with our findings.

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Personal Watercraft–Related Injuries

To the Editor.—The report of watercraft-related injuries by Dr Branche and colleagues[1] was timely but omitted discussing the impact of increased speeds on increasing the toll of dead and injured from personal watercraft (PWC).

Kinetic energy is the pathogen of PWC injuries.[2] Watercraft injury exposure-outcome relationships are governed by Newtonian laws of motion and kinetic energy. As in motor vehicle crashes, small increases in speed mean increases in actual traveling speeds, increased crash fatality risk, and large increases in death tolls.[3] Case fatality increases to the fourth power of the increases in watercraft impact speeds. A 10% increase in impact speed translates into a 40% increase in case fatality.[4] Injuries and deaths to both the watercraft drivers and bystanders occur disproportionately among the very young or intoxicated.[5]

In their article, Branche et al point to the 4-fold increase in injuries from PWC between 1990 and 1995. Watercraft offer no protection from impact to the driver or the bystander. There are no federal laws governing the safe conduct of these vehicles. Many of the injuries involve swimmers and other unprotected water enthusiasts. The impact of a PWC on a swimmer can be equivalent to a pedestrian being hit by a small truck.

The presumed recreational benefits of unrestricted and unrestrained PWC travel at high speeds are obtained for many at a significant cost in injury and mortality and at an enormous cost to society. For injury prevention programs to succeed and have a significant impact on reducing PWC injury toll, we must start by separating these vehicles from unprotected bystanders. Analogously, the major improvement in protecting pedestrians and bicyclists from moving vehicles has come from separating them from moving vehicles.[6]

As many of these injuries involve young and inebriated drivers and bystanders, it is necessary to educate the public about the inherent dangers of PWC, and to encourage supervision of minors. Specific training should be required. The manufacturers of these vehicles, similar to manufacturers of motorcycles and all-terrain vehicles, must be made aware and accountable for the potentially fatal combination of light-weight and inexpensive vehicles, fast speeds, and inexperienced young drivers. State and federal laws must be enacted to protect the operators of these vehicles and the innocent bystanders. Hel-

mets, life vests, and protective clothing for watercraft drivers and occupants must be mandated and enforced. Yamaha, the main manufacturer of PWC, recommends (Yamaha Website, yamahausa.com/wv1/safety, accessed September 15, 1997) that these vehicles be used by operators 16 years and older with a valid driver's license.

We suggest that watercraft injury prevention without speed restriction and mandatory specific PWC training and protective equipment is equivalent to driving a convertible on an undivided 2-way road, without seat belts or brakes, unencumbered by speed limits, and undeterred by laws or enforcers.

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In Reply.—It is unfortunate that we will no longer be able to monitor injuries associated with PWC because the data collection system that we used in our analysis, the National Electronic Injury Surveillance System, maintained by the US Consumer Product Safety Commission, no longer collects these data (Art McDonald, oral communication, September 9, 1997).

We agree with Dr Barach and Mr Baum that specific training for PWC users would be appropriate and that parental or adult supervision is recommended for minor children who are using PWC. We would emphasize again that personal flotation devices should be worn by all boating vessel operators and passengers, including those on PWCs on all waterways.

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18 Tender Points and the "18-Wheeler" Sign: Clues to the Diagnosis of Fibromyalgia

To the Editor.—A common question asked by rheumatologists of their patients is, "How do you feel in the morning?" This question may refer to morning stiffness from inflammatory joint disease or restoration from the night's sleep in fibromyalgia. Fibromyalgia is common (2% to 5% of the population in a recent study[1]) and underdiagnosed as a cause of chronic fatigue, achiness, cognitive dysfunction, and irritability.[2] Approximately 2 years ago, one of us (L.H.S.) noted that fibromyalgia patients often responded to this question with the answer, "I feel like I was hit by a Mack truck"; some did not specify the truck manufacturer, and others substituted bus or train. We determined the frequency and specificity of this finding, which could be referred to as the "18-wheeler" sign, as a clue in the diagnosis of fibromyalgia.

All patients seen in initial consultation at The Lyme Disease Center and The Lupus Clinic at Robert Wood Johnson Medical School, New Brunswick, NJ, were asked, "How do you feel when you wake up in the morning?"—no patients were provided any leading hints as to a desired response. Patients seen were then categorized as having fibromyalgia (meeting the American College of Rheumatology 1990 criteria for the diagnosis of fibromyalgia, which includes the presence of at least 11 of 18 defined tender points[2]) or a syndrome resembling fibromyalgia (not having a sufficient number of tender points to satisfy the criteria but having chronic fatigue, historical evidence of sleep disturbance, and cognitive dysfunction) or another rheumatologic syndrome (including systemic lupus, anticardiolipin antibody syndrome, rheumatoid arthritis, polymyalgia rheumatica, osteoarthritis, psoriatic arthritis, and Reiter syndrome).

From September 22, 1995, through November 20, 1996, we saw 93 patients with fibromyalgia, 77 with a fibromyalgialike syndrome, and 202 patients with other rheumatologic diseases or no definable abnormalities (eg, asymptomatic patients referred for evaluation of an isolated positive antinuclear antibody test or positive anti–*Borrelia burgdorferi* antibody assay). In this group of 372 patients, 42 (45%) of the 93 in the fibromyalgia group, 29 (38%) of the 77 in the fibromyalgialike group, and 18 (9%) of the 202 in the other group were referred for evaluation of Lyme disease or "chronic Lyme disease."[3] Although the primary focus of the evaluation of these patients was not chronic fatigue syndrome, for persons with a history of the syndrome, physical examination focused on the presence of fever or chills, sore throat, painful or nontender adenopathy, muscle pain or weakness, headache, arthralgia, and the rapidity with which the main symptom complex had developed. No patient was explicitly diagnosed as having chronic fatigue syndrome according to the Centers for Disease Control and Prevention definition then in use.[4]

The "18-wheeler" sign was present in 30 (42%) of 93 patients in the fibromyalgia group, including a patient with underlying lupus in whom fibromyalgia had not been suspected; none of the patients in the other 2 groups had a positive "18-wheeler" sign. None of the 77 patients with fibromyalgialike disorder or the 202 patients with other rheumatologic disorders had a positive "18-wheeler" sign ($P<.001$; Fisher exact test).

Further studies will be needed to determine if this historical feature is present in other conditions associated with chronic fatigue, eg, chronic fatigue syndrome, cancer, or hypothyroidism. Given that patients with chronic fatigue syndrome commonly satisfy criteria for the diagnosis of fibromyalgia (and vice versa), it is quite likely that the "18-wheeler" sign will be present in some patients with chronic fatigue syndrome. Nonetheless, as a clinical marker of fibromyalgia (whether or not in conjunction with chronic fatigue syndrome), the "18-wheeler" sign appears to be a specific, although not very sensitive, historical marker for the clinical entity fibromyalgia and may be useful in suggesting consideration of fibromyalgia.

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CORRECTION

Error in *P* Values.—In the Original Contribution entitled "Trends in Antimicrobial Drug Prescribing Among Office-Based Physicians in the United States," published in the January 18, 1995, issue of THE JOURNAL (1995;273:214-219), errors occurred in the reporting of *P* values. In Table 3, the *P* value for age younger than 15 years should be .04; in Table 4, the *P* value for cephalosporins (for blacks) should be .03. Other published *P* values changed somewhat in recalculations, but did not affect statistical significance. Exact *P* values not provided here are available on request from the authors.