Interferon beta treatment of multiple sclerosis

To the Editor: Like all neurologists, I eagerly look forward to the day when I can offer my MS patients more than a sympathetic ear and symptomatic treatment. I was trained by neurologists who viewed with great caution any therapeutic claims for MS, and I continue to retain a healthy skepticism while reading the literature and listening to my academic colleagues.

The most interesting part of Dr. Arnason's editorial¹ regarding the use of interferon beta-1b (IFNB) in the treatment of MS^{2,3} was not the "news" that interferon seems to work, but that so much of the editorial was devoted to explaining to those of us who evidently don't understand the statistics why it was that there was almost no difference in the clinical outcomes at 3 years.

It would be nice to think that we would be doing more than just producing better pictures after years of undoubtedly expensive (though apparently benign) injections.

A half a loaf is better than no bread—but are we really only being told that the bread we are not eating has a better aroma?

David I. Markovitz, MD

Palos Heights, IL

To the Editor: In the April 1993 expedited publication,² "Interferon beta-1b is effective in relapsing-remitting multiple sclerosis," the final sentence of the abstract states, "IFNB is the only treatment that has substantially altered the natural history of MS in a properly controlled clinical trial." This is a false statement.

The results of the trial of copolymer 1, reported in 1987 by Bornstein et al,⁴ showed a greater reduction in exacerbation rate, a greater percentage of patients free of exacerbations, and a greater overall reduction of the development of disability, with milder side effects. The study was "properly controlled." George Ellison⁵ described it as "the major milestone over the past 20 years in trial design for MS."

Every contribution to the understanding and treatment of MS is welcome. The two study groups^{2,3} are to be congratulated on their contribution, particularly the MRI analysis by Paty and Li et al,³ but that does not justify denial of the contribution of others nor does obscuring such contributions facilitate further work.

Quentin B. Deming, MD

Hanover, NH

To the Editor: I would like to congratulate Dr. William Sibley and his Multiple Sclerosis Study Group for publishing their results in *Neurology*.^{2,3} Too many important articles are published in journals mainly for the publicity that will be brought to the authors rather than for the purpose of directing the data to the specialists concerned with the specific disease process.

It is refreshing to note that we do have neurologists whose primary concern is to disseminate information to the specialists.

Lowell G. Lubic, MD

Pittsburgh, PA

To the Editor: We were excited to read the results of the IFNB study for relapsing-remitting MS reported by the IFNB Multiple Sclerosis Study Group.^{2,3} As active clinical investigators in the areas of cerebrovascular disease and neuromuscular disease, we are aware of the difficult methodologic issues that can arise in the interpretation of study results. Because of the pivotal nature of this study, we would appreciate it if the study investigators could clarify some additional questions.

1. *Why was the annual rate of exacerbations and proportion of exacerbation-free patients chosen at the beginning of the study as the primary efficacy end points?* Although prevention of exacerbations is a worthwhile goal, the primary objective of any

therapy for MS is to limit deterioration in neurologic function and to prevent disability. A change in the Kurtzke Expanded Disability Status Scale (EDSS) or the Scripps Neurologic Rating Scale would seem better suited for meeting this objective, although it would probably be a less sensitive end point for detecting a treatment effect. The study did not show any significant change from baseline in either of these scale measures for any of the three treatment groups. Exacerbations are primarily based initially on the patient's observations. Since IFNB has noticeable and frequent side effects, patient unblinding is a critical issue to address in the interpretation of the study results (see below).

2. *Analyses used an "intent-to-treat data set."² Does this mean that all patients who withdrew from a treatment arm continued to be regularly examined until completion of the study? Or were only the examinations prior to withdrawal used in the analyses?* If the latter is true, potential biases may be present, particularly since 17% of all study participants withdrew prior to completion of the study at 2 years, and 32% withdrew prior to 3 years. For example, withdrawals due to drug toxicity in the high-dose group would likely occur very early in the study. These patients would be less likely to have deterioration in neurologic function than patients who remained in the study for 3 years. Thus, the high-dose group may be more likely to have a better neurologic disability score simply because some of them were in the study for only a very short time. Survival analyses were used to compare annual rates of exacerbations between groups. However, this analysis assumes that the rate of exacerbations among withdrawals for a given treatment group is similar to that of patients who remain in the study. This assumption needs to be tested.

3. *This is a "double-blind" study. We applaud the pains taken to have a blinded patient examiner and assume that all examinations used to determine whether an exacerbation had occurred were done by the blinded investigator. However, since over one-half of patients treated with IFNB had injection-site reactions or flu-like symptoms, it is possible that more than one-half of patients were unblinded.* Side effects of the medication would have been discussed in detail as part of the informed consent. *What proportion of patients treated with IFNB had persisting side effects as the study progressed?* This question is important not only with respect to effectiveness of blinding but also for the quality of life in patients who may take IFNB in the future.

Did the investigators try to measure the degree of unblinding that occurred? The authors state in the Discussion that patients and study investigators are still blinded. However, investigators and patients can be asked what treatment they thought the patient was on without unblinding either investigators or patients. The overall effectiveness of blinding in each treatment group could be reported without unblinding of individual patients or investigators. These data are important for the proper interpretation of study results.

4. *The imaging data is quite supportive of a positive drug effect. However, early dropouts of IFNB patients could affect MR results just as they can affect comparisons of change in neurologic function in the various treatment groups. How were the MR images analyzed in those patients who withdrew from the study? Also, was the 10% change in lesion area chosen as a criterion at the beginning of the study or after analyses of the data?*

The data indicate that the lesion burden of the entire brain in the placebo group increased by a median of 2 cm² during 3 years. If this lesion area was concentrated in one brain location, it would correspond roughly to a "lacune" or hole of only 1.6 cm in diameter on a single 1-cm CT slice. Thus, given the relatively small amount of change in lesion area, it is not surprising that the overall disability in the placebo group did not significantly change over time.

Joseph P. Broderick, MD

Frederick J. Samaha, MD

Cincinnati, OH

To the Editor: The recent report on the clinical trial of IFNB² raises questions about the study's internal and external validity. Intention-to-treat analysis is claimed but not clearly presented. Such an analysis would ideally account for all patients over the course of the study regardless of what happened after randomization. Particularly confusing are the results presented in table 3 and subsequently duplicated in figures 1 and 2 of the article. In the report of the 2-year data, 34 patients are missing, and it is unclear whether complete information on the outcomes is available on those remaining. The report on 3-year data adds to the confusion, with table 3 indicating that no patients are missing but the text stating that 122 patients did not finish the third year. The lack of information on which patients were excluded or withdrawn in these analyses makes the interpretation of the results, as presented, impossible.

In addition, given the differential frequency of side effects, especially inflammation at the injection site, the study cannot be considered a double-blind trial. Two neurologists evaluated the patients, one unaware of drug side effects. Who determined the outcomes presented in the report? Outcomes assessed by the "treating" neurologist who was aware of drug side effects should be discounted. Did the treating neurologist influence decisions about hospitalization? Also, were the patients and neurologists kept ignorant of the findings on the MRIs? Knowledge of these results could influence the reporting of symptoms and the elicitation of signs. However, if the treatment affected only imaging characteristics and not the clinical course of the disease, by whatever measure, the treatment would be useless to patients.

None of the data on the slightly worsened EDSS score in all treatment groups are provided, but they are said to show no significant differences in the mean score between groups. What type of analysis was used to reach this conclusion? A reduction in exacerbations combined with no differences in deterioration across treatment groups could be interpreted as indicating that the active treatment, on average, reduced the frequency of exacerbations but lessened recovery from exacerbations. Also, how many patients developed a relapsing progressive or chronic progressive course in each treatment group?

With respect to external validity, no information is provided on the number of patients with MS who were screened at the 11 participating medical centers to obtain the 372 patients who were enrolled in the study. We hope that the answers to these questions will allow us to share others' enthusiasm about this promising treatment.

*W.T. Longstreth, Jr., MD, MPH
Gary M. Franklin, MD, MPH
Seattle, WA*

To the Editor: We were most interested in the recent papers^{2,3} demonstrating the favorable clinical and MRI findings associated with IFNB for the treatment of relapsing-remitting MS. The scope, experimental design, and follow-up of the studies were impressive.

One issue raised by Dr. Arnason in his editorial¹ (same issue) relates to the determination of the specific population of patients who might benefit from treatment with IFNB—specifically, what advice to give patients with either a first attack or exacerbating-progressive disease. Obviously, these questions warrant further prospective investigation, but data from the present studies might be reanalyzed to shed further light on these issues.

Even though the patients studied had relapsing-remitting MS, some had higher disease loads (as measured by initial MRI, EDSS, or duration from initial diagnosis). Were there any significant disease load-by-treatment group interaction effects evident in the ANOVAS? For instance, were those patients in both the 1.6-million international unit (MIU) and 8-MIU dose groups who appeared to benefit most (ie, had decreased MRI lesion areas, EDSS stability, or EDSS improvement) those with more or less disease load initially? More benefit in those with lower disease loads may provide preliminary evidence that would support initiation of earlier treatment.

Again, thank you for these valuable contributions, and we

anxiously await future work which will further elucidate the role of IFNB in MS.

*Mary A. McDonald, PhD
Craig M. McDonald, MD
Sacramento, CA*

To the Editor: We have reviewed the published results of the multicenter trial of IFNB in MS² as well as the accompanying MRI analysis³ and editorial¹ and agree that this therapy appears to be a significant development in the management of patients with autoimmune demyelinating disease. Several questions related to IFNB treatment were not, however, addressed in these publications.

Of most concern is that this trial, although purportedly an "intent-to-treat" study, did not report on the clinical or MRI status of withdrawn patients, either when they dropped out or at the time of study completion. The majority of patients withdrawing during the first 2 years were in the groups receiving IFNB (23 placebo compared with 42 IFNB), and many patients (122) did not complete the 3 years of the trial. We were not given information about disease activity as measured by relapse rate, EDSS, or MRI for these patients and thus have no basis for comparison of this group to others remaining in the trial. If patients doing poorly were less tolerant of side effects, treatment failures may have been lost to analysis. This may significantly alter efficacy analysis, as 15 of 16 of patients withdrawing apparently because of side effects were receiving IFNB. The potential impact of these dropouts on the 3-year data (including hospitalizations) must be discussed. After the second year, patients were given the choice of continuing in a third year of the trial and therefore, from this point, the trial was no longer truly randomized.

We disagree with the editorial statement¹ made by one of the blinded evaluators, Dr. B. Arnason, that "perhaps the effect on disability has been understated since treatment failures, most of them in the placebo arm, were lost from the study early on, and their fate is unknown." This implies that relapse rate correlates with eventual disability. Natural history studies have not demonstrated a correlation between relapses and outcome except when controlled for age and disease duration. We therefore cannot accept that relapse rate is necessarily an outcome predictor in this patient group. In the absence of follow-up disability scores and MRI data on withdrawals, a significant opportunity to clarify the true benefit of this drug has unfortunately been lost. Parenthetically, Dr. Arnason's statement¹ confirms that an intent-to-treat analysis was not performed.

We are also concerned about the adequacy of "blinding" for both investigators and trial participants, particularly in light of the significant placebo effect demonstrated in other therapeutic trials in MS. IFNB appears to have a significant systemic effect (fever, flu-like symptoms, headache, nausea, and skin reaction at the injection site) to unblind patients and blinded evaluators alike. We request that the authors clarify the severity and duration of these adverse effects in each treatment arm (eg, proportion of patients with injection site reactions and flu-like symptoms at 6, 12, and 18 months). It is stated that "the efficiency of evaluating-neurologist blinding in the study was excellent"; however, most investigators we have spoken to were not asked to reveal their opinion about the treatments received by their patients. We do agree that "the exact efficiency of investigator and patient blinding must be the subject of a later report"; however, we suspect that "blinding" will not be as efficient as claimed. The MRI data in this circumstance perhaps give a more objective view of the efficacy of IFNB.

There were other questions in our minds about the study in the general context of industry-supported, large, multicenter trials where central data handling is an issue. Was raw data available to all the investigators for their evaluation or were other steps taken to ensure impartial central evaluation independent of the trial sponsor? The actual level of industry involvement in data analysis and steps taken to ensure objective independent evaluation should be clarified in this and similar trials.

Finally, we agree with the decision to expedite publication of these important results. It would be advisable for the editor-in-chief to provide an accompanying written justification of the

decision to deviate from the normal publication process in instances like this. This statement should specify what factors affected the decision and what steps to ensure impartial peer review were nonetheless taken before publication. This would reassure readers that expeditious publication can still be accomplished with peer review despite our urgent timetable for finding effective treatments for MS.

L. Metz, MD, FRCP(C)
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To the Editor: The purpose of this letter is to advise the neurologic community not to embrace Betaseron (IFNB) as *the* drug for MS, and to recommend that we keep our minds very open on this very expensive agent that has no demonstrable effect on disability in MS. I remain skeptical about the drug's utility despite the extraordinary publicity being generated, and am very worried that the millions of dollars that will be spent on this agent will be money that could have been used more wisely.

Why do I feel this way? First, the atmosphere in which the drug was developed and in which it will be marketed is a charged one that will prevent careful analysis in the future of its efficacy. Neurologists and MS patients are continually frustrated by their impotence to deal with this devastating illness, and any potential help is gratefully accepted, especially if it comes under the rubric of a recombinant protein. Biotechnology companies are eager for a profitable product to regain some of the lagging enthusiasm for investment of large amounts. The FDA wants to provide a product for a disease as crippling and unrelenting as MS. Thus, it is likely that, once Betaseron is used, any pleas for careful analyses of its utility will fall on deaf ears.

Second, the studies of Betaseron^{2,3} were, on balance, not dramatically convincing. Disability, which neurologists are comfortable in measuring, was not affected. MRI abnormalities seemed to be decreased in the treated group, yet the quantitation of MRI findings in MS remains a controversial topic, and we all feel uncomfortable in following MS by MRI. There was a greatly increased incidence of inflammatory events in the skin in the treated group, raising the possibility that the treated patients (or their physicians) were not blinded. It is also possible (*cf* bee venom) that any protein injected into the skin with subsequent inflammation will result in decreased MS exacerbation.

Third, Betaseron had absolutely no demonstrable effect on disability, the major complaint of MS patients. It would certainly have been appropriate to continue the study to assess effects on disability over a longer period, since one would predict that a significant effect of decreasing the activity of the disease would result in decreased disability.

Fourth, almost nothing is known about the effects of Betaseron once injected. There is no evidence that it even enters the CNS. We know nothing about how long it lasts in the circulation since reliable assays for it have not yet been developed. It is possible that it is degraded within minutes of injection. It is clear that anti-Betaseron antibody develops in injected humans, but its measurement was poorly performed in the study; it is possible that repeated injection leads to high levels of neutralizing antibody.

Finally, the medication is likely to be extraordinarily expensive. In an era of increased cost-awareness, this is not a minor problem.

So what should we do? My recommendation is that Berlex Laboratories be required to use most of its profits to fund a long-term study administered by groups selected by the National Multiple Sclerosis Society, which will test the effects of Betaseron on disability and answer some of the above nagging questions. If the company refuses to do this, the medication should not be used until disability studies are available from another group of investigators currently studying the medication. If there are no clear effects on disability, and it remains expensive, it should be summarily dropped from our armamentarium.

Andrew R. Pachner, MD
(former member of the External Advisory Committee
for the assessment of Betaseron in MS)
Washington, DC

To the Editor: The demonstration by the IFNB Multiple Sclerosis Study Group² that interferon beta-1b reduces MRI lesions, decreases exacerbation rates, and results in a reduction in hospital stays is certainly of great interest. However, the failure to demonstrate a significant effect on disability ratings ($p = 0.161$ at confirmed end point) raises some clinical concerns. It is difficult to share Dr. Arnason's conclusions in his editorial¹ in the same issue that a favorable effect of IFNB on disability has been shown.

The MRI improvement does not necessarily translate to improvement in level of function. The decline in exacerbation rates may be of some modest benefit, although if it does not translate into practical improvement, it's hard to see its advantages. The decrease in hospital days may be of some economic benefit, although, because of the availability of high-dose intravenous steroids on an outpatient basis, it is rare in my clinical practice that ambulatory MS patients with exacerbations need to be hospitalized.

On the other hand, the cost of IFNB is estimated by the manufacturer at \$9,000 a year, not including the laboratory costs of follow-up to identify leukopenia and liver function abnormalities. Additionally, in the material the manufacturer recently sent to me (and presumably to all neurologists) by express mail, they report one suicide and four suicide attempts in the active treatment group. This was not noted in the above article.² It would seem that the cost-benefit ratio for this new treatment is not convincing enough to warrant its use in clinical practice.

J.A. Klapper, MD
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Reply from the Authors: Several of the letters reflect the long-held "healthy skepticism" of Dr. Markovitz and other clinical neurologists about treatment in MS. We appreciate the perceptive comments; MS patients should be reassured that critical minds are alert to protect their interests. Reasonable answers can be given to most of the questions now, but poststudy subset analyses continue, and answers to some of the questions will be made in a second response in the next few months.

The IFNB treatment trial results were unique because the drug in high dosage was associated with a four- to sixfold decrease in the numbers of new and enlarging lesions in the University of British Columbia (UBC) frequent-scan cohort,³ something never before seen in a controlled trial of any other agent in MS. Recall that the North American trial of cyclosporine in chronic progressive MS was also monitored by MRI by UBC radiologists, with no differences seen between placebo and cyclosporine treatment. Since most studies have shown a close correspondence between MRI appearance and gross pathology, there is an inescapable inference that IFNB treatment probably limits new pathology in the brain. We feel this to be an outcome measure that could not possibly be clouded by issues such as blinding.

A common objection to the IFNB data is that it did not show a clear-cut ability to slow progression; some have even said that exacerbations are unimportant, and that only an effect on disability should be considered. As emphasized in the publications,^{2,3} however, the small effect in reducing disability is not surprising; in order to demonstrate prevention of disability, the placebo arm must worsen, an event exhibited by only a minority of this patient group. Indeed, the study was not designed nor powered to detect an effect on prevention of progression. Even with a population of 372 patients, composed largely of those with early low-disability MS, only 28% had advanced by one Kurtzke EDSS point at the end of 3 years. Dr. Pachner's statement that IFNB had "absolutely no effect on disability" is incorrect since, by comparison, only 20% of the group treated with 8 MIU of IFNB deteriorated by one EDSS point. This reduction in disability progression approximates the one-third reduction in exacerbation rate in the high-dose IFNB treatment arm. Apparent reduction in pathology, as judged by the MRI studies, is certainly cause for optimism that, with time, more treatment-associated reduction in disability will be shown. Also, different dosage regimens need study, since there was a suggestion of dose-response in the IFNB-treated patients in both the exacerbation rate and the MRI data.

Table 1. Dropouts in IFNB MS study: Numbers and reasons

	Placebo	1.6 MIU	8 MIU
Excess steroids	13	2	2
Prohibited meds.	2	0	0
Neurol. worsening: patient or doctor perception	5	7	10
Noncompliance	2	3	3
Entry violation	1	1	1
Pregnancy	1	1	0
Adverse event	1	6	10
Miscellaneous	5	13	2
2-yr completion	7	10	5
3-yr completion	2	5	2
Totals	39	48	35 = 122

In answer to Drs. Longstreth and Franklin, 462 patients were screened to enroll the first 338 participating patients; 45 patients were screened to enroll the last 34 patients. Neurologic outcomes were recorded by the evaluating neurologist; the treating neurologist recorded only side effects and medications; and either could make a decision to hospitalize. The local radiologist's report on the initial and annual MRI was returned to the patient's chart, as were all laboratory reports. There was no systematic attempt to inform patients of these MRI reports. Neither the neurologists nor the patients had knowledge of any quantitative MRI results prior to the External Advisory Committee's decision to offer all patients treatment with 8 MIU IFNB—shortly before submission of the manuscripts. The question about the numbers of patients becoming chronic progressive in each treatment arm cannot be answered now because some centers have not yet converted to open-label treatment and are still blinded. Detailed subset analyses incorporating a precise definition of "chronic progressive" are planned, and an answer to this important question will be forthcoming in a few months. Differential factors such as initial MRI lesion burden, EDSS, duration of disease, age, gender, geographic location, and viral infections will be examined.

In reply to Dr. Deming, there was no intent to diminish the contributions of others who have conducted clinical trials in MS. Perhaps we should have said that the evidence justified the statement that IFNB is the only drug that has altered the course of MS because of the MRI effects—not yet shown for copolymer treatment. Indeed, the 1987 copolymer trial results⁴ were apparently not entirely accepted because the trial is currently in the process of being repeated with some quantitative MRI monitoring.

Dr. Lubic's feeling that the results should be presented first in a journal read by neurologists was shared by many of the investigators and by the undersigned.

Drs. Broderick and Samaha are correct in questioning our characterization of the analysis of study results as "intent-to-treat." "Modified" intent-to-treat analysis of the data would have been more accurate. The aim of intent-to-treat analyses is to avoid any systematic influence on outcome by dropouts who behave differently for a given outcome measure than do those remaining in the study. We wish to assure Drs. Broderick and Samaha that all patients were included to the point of dropout. The initial protocol required only a 3-month follow-up period for dropouts, but this was changed to end-of-trial at the beginning of the third year. The study did conform to the "intent-to-treat" ideal in that all available data on all patients were included in the analyses. More complete information on the reasons for dropping out of the study is included in table 1, above. Further details and data will be made available on request.

Multicenter treatment trials rank high in the order of complex human activities. Patient accrual was staggered during the study. A full analysis of data was first made when 338 patients had completed a full 2 years in the study, as prescribed by the protocol. The 3-year data given in the publications^{2,3} included all 372 patients. (The FDA chose a different analysis for the package insert, analyzing the exacerbation rate at 2 years in all 372 patients—the figures

Table 2. Efficiency of blinding in the IFNB MS trial

	Placebo	1.6 MIU	8 MIU	1.6 or 8 MIU	Unknown
Blinded investigator guess (207 patients)					
Actual Rx					
Placebo	22%	8%	7%	4%	59%
1.6 MIU	19%	4%	10%	9%	58%
8 MIU	14%	11%	22%	11%	43%
Blinded patient guess (170 patients)					
Actual Rx					
Placebo	30%	22%	5%	14%	30%
1.6 MIU	23%	26%	9%	16%	26%
8 MIU	6%	27%	35%	18%	14%

are somewhat different but the conclusion the same, a highly significant difference in favor of the 8-MIU treatment group.)

Drs. Broderick and Samaha ask why the annual exacerbation rate and proportion of exacerbation-free patients were chosen as the primary efficacy end points. The exacerbation rate was chosen because exacerbations can be defined and measured, and, historically, it has frequently been used as an efficacy measure. Also, it was thought that its use might result in a shorter study, especially if there was MRI confirmation of benefit; this, in fact, occurred. The slow average rate of progression in the EDSS score in untreated relapsing-remitting patients requires studies of long duration in order to draw conclusions.

Systemic flu-like symptoms after injection decreased from 60% initially in the high-dose IFNB group to 10% over time, most commonly about 2 months; in the placebo group and low-dose groups, flu-like symptoms decreased from 30% to 13% over time. (In the open-label portion of the study, now ongoing, in which all patients receive 8 MIU, systemic reactions are largely suppressed by concomitant nonsteroidal anti-inflammatory drugs; the latter were not permitted in the blinded study.) Injection-site reactions decreased from 79% initially in the high-dose group to 47% at week 30. The evaluating neurologist did not ask about injection site reactions and did not become aware of them during examinations because patients did not completely disrobe, and in both men and women, the most common injection site (anterior thighs) was concealed by clothing.

A survey of blinded investigators and patients was made just before the end of the study to determine the degree of blindness achieved. A few centers remain blinded because they have not yet fully converted to the open-label phase. Results are available now for blinded investigator assessment of 207 patients and 170 blinded patient assessments (table 2). Our interpretation of these data is that the investigators were efficiently blinded, as were patients in the placebo and 1.6-MIU groups. Most patients on high-dose treatment guessed correctly that they were receiving interferon, even though their guess as to dose was no better than random. The investigators analyzing the MRIs were completely blinded, and again, the MRI results encourage us to believe that the incomplete blinding of the high-dose patients did not compromise the validity of the study.

All dropouts had an MRI at conclusion of treatment if they had not had one in the past 6 months, and these data were, of course, included in the MRI analyses. The display of some of the MRI data as "more . . . or less than . . . 10%" change was a decision made as the data were being prepared for publication in recognition of the difficulties still involved in quantitative MRI, because it was felt that most readers would be interested only in changes of at least that magnitude. The point made by Drs. Broderick and Samaha that the lesion burden in the placebo group increased only by a median of 2 cm² is factually correct but ignores the dynamic data from the frequent-scan cohort showing the striking decrease in new and enlarging lesions in IFNB-treated patients. This emphasizes the point that frequent-scan studies are probably much more important in judging the efficacy of treatments in MS than changes in lesion burden over long time intervals. Nonetheless, the changes in the total lesion burden also clearly showed the benefit of IFNB treatment.

Table 3. Exacerbation rates in MS patients with and without injection-site reactions from IFNB

Treatment	With injection-site reactions		Without injection-site reactions	
	No. pts	Exac. rate	No. pts	Exac. rate
Placebo	37	1.07	75	1.37
1.6 MIU	89	1.24	22	0.81
8 MIU	96	0.84	19	0.81

Dr. Klapper is concerned about the five suicide attempts in the study, one of which was successful. Three of these were in the 8-MIU group and two in the 1.6-MIU treatment arm. Sadovnick et al⁶ reported the suicide rate in MS patients to be about seven times higher than that in age-matched controls. Rabins et al⁷ found that depression in MS patients is at least partly determined by the brain lesions, since MS patients with brain lesions were more depressed than those with cord lesions only. In another large placebo-controlled trial of IFNB in 400 patients with AIDS, the frequency of depression was 16% in the placebo group and 14% in the treated group and there were no suicides, although one attempt occurred in the placebo group.⁸ These considerations make us favor the view that the suicide attempts in the IFNB MS study were MS-related rather than treatment-related. Nevertheless, caution and further observation will be necessary and patients should be notified of the study results, as mentioned in the package insert.

Dr. Metz and colleagues raise a question about industry-supported trials in MS. We agree that a second independent analysis of the raw data by a committee of study investigators would be preferable. Actually, a committee has been formed to investigate the feasibility of doing just this in future trials and obtaining funding for the effort from independent sources. In all fairness, however, it required considerable courage on the part of the involved pharmaceutical companies to invest large sums of money in hopes of discovering an effective treatment for MS. No studies of this magnitude could be financed by national MS societies and, in the present climate, are unlikely to be funded from federal sources.

Dr. Pachner's suggestion that anything producing inflammatory skin reactions might benefit MS could not be verified by subset analysis; the difference in exacerbation rate between high-dose IFNB and placebo patients was equally apparent in those patients without injection site reactions (table 3).

Dr. Pachner was a member of the External Advisory Committee that reviewed the data and unanimously recommended that the study be stopped and all patients treated with 8 MIU of IFNB. He also was given a copy of the manuscripts to review prior to publication and made no suggestions for change. His currently expressed skepticism is perhaps understandable in the context of the historically long and frustrating effort to achieve some convincing therapeutic success in this disease. The undersigned, however, we believe are representative of most of the investigators involved in the trial who believe that the study provides strong evidence that IFNB has a positive, beneficial effect in the treatment of relapsing-remitting MS. New clinical studies to study its influence in chronic progressive MS will start during the next few months.

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For the External Advisory Committee:
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Myopathy in congenital amaurosis

To the Editor: What Mrak et al¹ describe is not myopathy at all but a nonspecific and even normal ultrastructural finding. They describe "misaligned" thick filaments with "smearing of the A band" and "loss of distinct I bands." These occurred in "small foci . . . extend[ing] longitudinally only two or three sarcomeres." In the illustrations, these areas extend laterally only a few myofibrils. They occurred with rarity, at an average of 2.4 such foci per 3,400 μm^2 in a 0.0034-mm² area of one patient. This is an extremely small sampling.

Identical focal (and even more extensive) areas of thick and thin myofibril disruption with relative preservation of the Z disk ("myofibrillar disruption") occur in healthy normal adults² and can be seen commonly following intense eccentric muscle exercise.³ Such lesions can be reproduced experimentally in animals with myopathy due to emetine⁴ or ischemia⁵ and in experimental models related to severe isometric exercise⁶ where they occur predominantly in type II myofibers.⁶ More commonly, similar focal lesions are accompanied by or precede disintegration or streaming of the Z disk. This is probably the most common pathologic change in any disorder of muscle, common to numerous conditions, including denervation,⁷ tenotomy,⁸ ischemia,⁵ exercise,³ and even psychosis.⁹ It seems safe to say that myofibrillar disruption is entirely nonspecific pathophysiological. In fact, its presence only indicates an abnormality when its frequency is compared with that in appropriate age-matched and muscle-specific controls.

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Reply from the Authors: Careful attention to the illustrations in our article¹ and to the accompanying descriptions should allay the concerns of Dr. Kuncel, for the resemblances between the myofibrillar alterations in our patient and the alterations in the various conditions he refers to are rather superficial. The lesions in our patient, as well as those we recently described in a second patient,¹⁰ consist of loss of register of thick filaments along with some loss of parallel alignment of these filaments. Sarcomere length was only mildly altered; indeed, measurement and statistical analysis of sarcomere length was necessary to document any alteration in sarcomere length in our patient. Z-line alterations were similarly subtle, consisting of no more than occasional fine waviness of the Z line. We found not one sarcomere showing extension of Z-line material laterally into or across the I-band region ("Z-line streaming") in either of these two patients.^{1,10}

These two features (relative preservation of sarcomere length and Z-line integrity) distinguish the alterations in our patients from most of the conditions cited by Kuncel. Z-line alterations are in fact the most prominent feature in the sparse myofibrillar disruptions of normal muscle described by Meltzer et al² and Kuncel et al,⁶ in the focal alterations found in acutely psychotic patients,⁹ in the myopathy resulting from experimen-

tal phencyclidine administration,⁶ and in the alterations seen in muscle following intense eccentric exercise.³ Meltzer et al² did describe "focal and extensive myofibrillar disruption without Z band streaming" in 1 to 2% of fibers from 15% of normal patients. Even these lesions, however, showed fragmentation of the Z line (their figure 8 in reference 2), and 80% of these patients had Z-line streaming elsewhere in their biopsies. The ultrastructural appearance of target and targetoid fibers, whether occurring naturally in humans^{7,11} or experimentally as a consequence of Achilles tenotomy,⁸ is so different from the findings in our patients as hardly to deserve comment.

Marked hyperextension of the sarcomere (up to twice resting length) due to local or regional depletion of high-energy phosphorylated intermediates is a feature of several of the entities cited by Kuncel, including experimental emetine myopathy⁴ (in which the foci of myofibrillar disruption correlated with areas of decreased, histochemically demonstrable mitochondrial activity) and experimental ischemic myopathy.⁵ Our patients showed no abnormality of mitochondrial distribution or mitochondrial activity on histochemical (NADH-tetrazolium reductase) or ultrastructural examination.

Besides these qualitative differences in ultrastructural appearance, there are quantitative differences as well. Contrary to Kuncel's assertion that the lesions we describe "occurred with rarity," they were actually quite frequent in comparison with most of the small myofibrillar alterations cited by Kuncel. For instance, lesions occurred in 2 to 4% of muscle fibers in experimental emetine myopathy,⁴ in 2 to 8% of fibers of normal individuals,² and in 2 to 29% (mean, 4%) of acutely psychotic patients.⁹ In contrast, the lesions we describe were present in most fibers and were often numerous in individual fibers. Indeed, we quantitated these lesions per unit area rather than per fiber for this reason. The 0.0034-mm² (3,400 µm²) area that Kuncel derides as "an extremely small sampling" is in fact the area examined in each low-magnification electronmicrograph and not, as he implies, the total area of muscle examined. We found lesions in almost all these "extremely small" sampling areas. As stated in our article, we reviewed the ultrastructure of nine cases of "unstructured" congenital myopathy, in which small foci of Z-line streaming and myofibrillar disarray are well known.¹² We found no abnormalities of myofibrillar architecture in five of these cases. In the other four cases (one with type I predominance and three with normal muscle histochemical findings), we found a total of from 1 to 8 (mean, 5) small (involving 2 to 3 sarcomeres) foci of myofibrillar disarray in ten randomly selected, 3,400-µm² fields (average frequency of 0.5 lesions per 3,400-µm² field; range of 0.1 to 0.8 lesions per 3,400-µm² field). This is less than one-fifth the frequency of the qualitatively different lesions in our patient. In these nine patients, we found not one sarcomere showing loss of thick filament register (broadened A bands) of the type we described in our two reports.^{1,10}

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Subarachnoid hemorrhage

To the Editor: We read with great interest the article by Longstreth et al.¹ As a population-based series on subarachnoid hemorrhage, the study is outstanding since all admitted patients were investigated with CT. Unfortunately, the authors have not taken full advantage of the information CT provides. CT not only allows an accurate diagnosis of subarachnoid hemorrhage, but it can also distinguish an aneurysmal from a nonaneurysmal source of the hemorrhage. In their study, the authors have included patients in whom no aneurysm was found on repeated angiograms. Although some of these patients harbor an aneurysm, the vast majority have a nonaneurysmal subarachnoid hemorrhage.² This nonaneurysmal hemorrhage can be recognized by a characteristic pattern of hemorrhage on CT in which the blood is confined to the cisterns around the midbrain ("perimesencephalic hemorrhage").^{3,4} The natural history of this subset of subarachnoid hemorrhage strongly differs from that of aneurysmal subarachnoid hemorrhage: patients with a perimesencephalic hemorrhage are not at risk of delayed cerebral ischemia, rebleeds do not occur, not even after a long interval, and the outcome is invariably excellent.^{2,5}

Approximately 10% of all patients with a subarachnoid hemorrhage and approximately two-thirds of patients with an initial normal angiogram have a perimesencephalic hemorrhage.²⁻⁴ In the series of Longstreth et al¹ of 171 patients with subarachnoid hemorrhage, including 17 with repeatedly normal angiograms, the number of patients with a perimesencephalic hemorrhage can therefore be estimated at between 12 and seventeen.

If the patients with a perimesencephalic hemorrhage had been excluded from the study, the 1-month survival would have dropped from 68% to 64% and the percentage of patients with a good outcome from 52% to 46%. These changes are not dramatic, but if the purpose is to study fatality rates of subarachnoid hemorrhage and the influence of changes in medical treatment and aneurysm surgery, studies should no longer include patients with definite nonaneurysmal hemorrhage.

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Reply from the Author: We appreciate the comments of Drs. Rinkel and van Gijn. We have come to the same conclusion that many patients in whom an aneurysm cannot be found suffer from a different disease with a more benign clinical course and likely different etiologic risk factors than those in whom an aneurysm is found. Unfortunately, we do not have easy access to the CTs to determine how many patients in our recent study¹ would meet criteria for perimesencephalic hemorrhages.^{3,4} Five of the 17 patients who had a negative angiogram had no blood seen on the initial CT, but the scans were done a mean of 55 hours after the ictus. In these five patients, the diagnosis of subarachnoid hemorrhage was based on a typical clinical picture and CSF findings.

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Intracranial hypotension

To the Editor: Excluding the debatable case reported by Hochman et al,¹ three of the four cases of supposed low-pressure CSF headaches that have been published with MR images for review demonstrate gadolinium (Gd)-DTPA filling of the superior sagittal sinus (SSS) in addition to a greater than normal enhancement of the meninges in patients symptomatic from positional-type headaches. In contrast to the 46-year-old patient of Hochman et al, who had a rising CSF protein and no dural sinus enhancement despite intense meningeal enhancement, the classic example presented by Fishman and Dillon² had (1) a normal CSF protein, and (2) normal Gd enhancement of the SSS during the low-pressure headache phase and also in the recovery phase after the CSF leak at a T12-L1 arachnoid cyst had been patched. Two of three cases reported by Mokri et al³ had this expected pattern of both the dural sinuses and meninges enhancing yet had moderately elevated CSF protein. A third case of repeated shunt revision reported by Mokri et al, with a CSF protein of 649 and no dural sinus enhancement despite pathologically intense meningeal enhancement, raises the question of shunt-related meningeal fibrosis⁴ or partial block of Gd exit into the draining dural sinus. The latter concern is also raised about the case of Hochman et al¹ despite the absence of intracranial hypertension. In their patient, falcine and meningeal enhancement not only became more extensive and intense at day 9, but also the modest Gd enhancement of the SSS seen initially at day 2 was then lost. In addition, the unenhanced T₁ sagittal images of this 46-year-old patient with a history of meningitis displayed a hyperintense segment to the SSS at the convexity, suggesting postmeningitic fibrosis or even possible partial thrombosis of the SSS. Hochman et al are therefore referred to the paper of Ingstrup and Jorgensen,⁵ which demonstrated pathologically intense enhancement of the falx and meninges in a pattern very similar to the case in question in a surgically proven case of sigmoid sinus thrombosis.

Since sinus venous thrombosis can have mortality rates as high as 15% overall with a higher 69% mortality rate when there is associated intracranial hemorrhage,⁶ it is important for neurologists to recognize the disorder and distinguish it from intracranial hypotension by both clinical and radiologic criteria in patients with acute, severe positional headaches and diffusely intense meningeal enhancement. To thoroughly evaluate the possibility of a partial SSS thrombosis when intense meningeal enhancement is noted, it is therefore recommended that the nonselective 180° refocusing pulse/single-section spin-echo method be used to rule out artifactual hyperintensities in the SSS on the precontrast T₁ image.⁷ The normal patterns of contrast enhancement within the meninges, falx, and dural sinuses are shown (figure) for MRI using a subtraction technique.⁸ The most definitive noninvasive evaluation is achieved by phase-sensitive gradient-echo MRI.⁹

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Figure. After densities of the noncontrast scan are subtracted from the postcontrast image, the normal pattern of diffuse meningeal, falcine, and dural sinus enhancement can be visualized. Pre- and postcontrast coronal T₁ MR images were used to generate the above subtraction image from a 45-year-old man with no intracranial pathology (TR = 600 msec, TE = 20 msec; 20 ml of IV Gd-DTPA given).

Reply from the Authors: Dr. Meyer has questioned the diagnosis of spontaneous intracranial hypotension (SIH) in our patient because the MR images do not “demonstrate persistent gadolinium (Gd)-DTPA filling of the superior sagittal sinus in addition to a greater than normal enhancement of the meninges.” He suggests instead that our patient had SSS thrombosis. This is incorrect. Dr. Meyer’s criteria for SSS thrombosis are flawed. The exact signal within the SSS depends heavily on the parameters chosen for MRI. With the equipment and image series used in our hospital, patent venous sinuses typically display absence of Gd-DTPA opacification or only central (fast-flow zone) filling of the SSS. His false criterion of SSS thrombosis has led him to misinterpret the published images.

Panullo et al¹⁰ recently described the MRI changes in seven patients with intracranial hypotension (IH). Clinically, each of the six in whom a lumbar puncture was performed had low CSF pressure. Each had diffuse meningeal enhancement (DME). Three patients had subdural effusions; six had measurable descent of the brain. No patient had SSS thrombosis. These authors¹⁰ did not describe Gd-DTPA filling of the SSS in any of the seven patients. Review of their published MR images indicates absence of Gd-DTPA filling of the dural sinuses at the torcular (axial image of patient 1) and absence of Gd-DTPA filling of the SSS and of the straight sinus in patients 3 and 4. These cases further contradict Dr. Meyer’s contention and support the validity of our report.

Addressing the same issue from the clinical standpoint, review of 27 patients with angiographically confirmed SSS thrombosis¹¹ revealed headache in 48% and increased intracranial pressure in 44% of patients. No case exhibited postural exacerbation of headache or low CSF pressure. The clinical features observed in our case are inconsistent with SSS thrombosis but wholly consistent with SIH with DME.

Therefore, we reject Dr. Meyer’s challenge of our case. We conclude that (1) DME can occur in IH without or with only incomplete Gd-DTPA filling of the SSS. (2) DME is not pathognomonic of IH, as was recently illustrated by a patient with paroxysmal nocturnal hemoglobinuria with DME and angiographically confirmed SSS.¹² (3) DME must be associated with low CSF pressure before this MRI appearance can be attributed to IH. (4) DME in IH is confined to the pachymeninges, as we pointed out in our paper.¹ (5) DME in IH is most likely secondary to dural venous hyperemia that occurs in response to low CSF pressure. CSF is normally resorbed down a pressure gradient from the subarachnoid space across the arachnoid villus to the dural sinus lumen.^{13,14} With low CSF pressure, as occurs in

IH, maintenance of this gradient would require a decrease in dural venous sinus pressure. The dura has a rich vascular plexus even away from the venous sinus.¹⁵ Dilatation of the dural venous system in response to low CSF pressure could reduce intrasinus pressure and appear as DME on MR images. Documentation of low CSF pressure and correspondingly reduced SSS pressure by simultaneous measurements would support this hypothesis and, perhaps, provide a test for the diagnosis. (6) DME in IH is not secondary to a disruption of the blood-brain barrier, since the dura is outside this barrier. (7) DME is not secondary to inflammation of the dura. Indeed, a second patient with SIH and DME recently studied by us had normal dural biopsy. (8) DME in IH is unlikely to result from tearing of small blood vessels (which was recently suggested as an alternative hypothesis¹⁰) given the diffuse extent and the extreme symmetry of the enhancement.

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Nonvasculitic neuritis

To the Editor: We enjoyed reading the recent article by Logigian et al¹ describing nonvasculitic mononeuritis multiplex. We have been treating a similar patient for more than 3 years.

A 74-year-old woman presented in February 1990 because of progressive lower-extremity weakness over 3½ months, leading to wheelchair dependence. She also had numbness of her feet and fingers. Right-sided abdominal pain had been present for 6 months, extending from the spine to below her breast. Two abdominal surgical procedures failed to relieve the pain. She

Figure. Sural nerve biopsy showing inflammation within perineurium, endoneurium, and surrounding small epineurial vessels. Lymphocytes predominate, with occasional small groups of epithelioid histiocytes (bar = 50 μ).

had lost 35 pounds over 3 months because of poor appetite.

Examination showed complete paralysis of right ankle dorsiflexion and moderate weakness on the left. Weakness of other lower-extremity muscles was moderate-to-severe on the right and mild on the left. Upper-extremity strength was normal. Deep-tendon reflexes were present, except for the right ankle jerk. Skin was hypersensitive in the right T-6 dermatome, and there was distal sensory loss in the lower extremities. There was no rash, organomegaly, enlargement of lymph nodes, or ocular abnormality.

CBC, routine blood chemistry, calcium, angiotensin converting enzyme, serum protein electrophoresis, sedimentation rate, fasting blood sugar, thyroid function tests, chest x-ray, CT of the abdomen and pelvis, and gallium scan were normal. CSF was normal except for a protein of 75 mg/dl. Pulmonary function testing showed a mildly reduced diffusion capacity (single-breath DL_{CO} , 13.6 ml/minute/mm Hg; normal, >17). The patient showed no response to PPD or control skin testing. Nerve conduction studies and EMG indicated axonal polyneuropathy.

Sural nerve biopsy (figure) showed focal areas of granulomatous inflammation, primarily within perineurium, and around endoneurial capillaries. Focal areas of necrosis within the endoneurium of one fascicle were present. Ziehl-Neelsen and Fite stains for acid-fast bacilli were negative. Electron microscopy showed an aggregate of epithelioid histiocytes near an endoneurial capillary. Degenerating axons were noted. No organisms were seen.

The patient was begun on prednisone, 60 mg daily, and hydroxychloroquine, 200 mg twice a day. She gradually improved over the next 2 months, and her prednisone dose was gradually reduced. The right-sided abdominal pain completely resolved. After 3 months, she was taking 40 mg of prednisone on alternate days, and proximal lower-extremity strength was normal, but distal weakness was only slightly improved. She was able to ambulate independently, and her appetite returned. After 1 year, examination was normal except for mild gait imbalance and hyporeflexia. She has remained stable, with minimal disability, but continues to take 300 mg of hydroxychloroquine and 10 mg of prednisone on alternate days (she felt that further reductions produced weakness).

Our patient's benign clinical course and failure to develop evidence of systemic illness over more than 3 years is evidence against lymphoma or unrecognized leprosy (both of which might temporarily improve with corticosteroid treatment).

We wonder whether this might represent a restricted form of sarcoidosis. Our patient did have an abnormal DL_{CO} and cutaneous anergy. The pathology is similar to that reported in neuropathy due to sarcoidosis, in which the perineurium is also commonly involved. Evidence for systemic sarcoidosis in these cases has also been scant (only one of six that we reviewed had an abnormal chest x-ray).² By analogy, patients with idiopathic granulomatous inflammation restricted to the meninges or

brain are often thought of as having a form of sarcoidosis. We recently treated another patient with similar pathology who also had a transient erythema nodosum-like rash on her shins, a mildly elevated ACE level, and abnormal liver function tests. She also has done very well over approximately 4 years, never developing any other evidence of systemic illness.²

From a practical standpoint, it is important to recognize that these patients can have a good long-term clinical outcome when treated.

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To the Editor: We read with interest the article by Logigian et al.¹ We wish to add another patient with idiopathic, predominantly sensory perineuritis and mononeuritis multiplex.

This 63-year-old man noted painful paresthesias in the right foot, then, 5 months later, in the left leg. By June 1992, he had involvement of the left chest, arm, and face. On examination, there were discrete areas of cutaneous sensory loss across both arms and legs up to the elbows and knees, with normal position and vibration sensation. Cranial nerves, motor strength, and coordination were normal. Tendon reflexes were absent at the ankles but present elsewhere. The following studies were normal or negative: chemistries, including CK, CBC, B₁₂, thyroid functions, serum immunofixation electrophoresis; GM₁, myelin-associated glycoprotein, Hu, and human T-lymphotropic virus type 1 antibodies; chest radiograph, brain CT, and cervical and lumbar spine MRI. The antinuclear antibody titer was 1:80 speckled. The peripheral blood CD4:CD8 lymphocyte subset ratio was 4.8 (normal, 1.4 to 2.8). CSF was under normal pressure with one mononuclear cell, normal protein, glucose, cytology, VDRL, and absent oligoclonal bands. Motor nerve conduction studies were normal. Sensory nerve action potential amplitudes were reduced. Needle electromyography showed no spontaneous activity.

Sural nerve biopsy showed dense, nonmalignant perineurial infiltration composed of lymphocytes that expressed CD2, CD3, CD5, and CD7 T-cell antigens with rare CD22-positive B cells, with a CD4:CD8 subset ratio of 6:1. There were no abnormal immunoglobulin deposits. Semithin sections showed a mild decrease in large myelinated fibers. A biopsy specimen of the gastrocnemius muscle showed neurogenic atrophy without inflammation.

The patient was treated with three courses of IV methotrexate, 70 mg, and oral dexamethasone, 24 mg, and by the third week there was dramatic improvement in the dysesthesias. He was placed on prednisone, 40 mg orally, alternate daily for 8 months. This was tapered off with sustained improvement and only residual symptoms 4 months later.

Neurolymphomatosis (NL), so cited by the authors,¹ requires differentiation from perineuritis. Two points relating to NL merit comment.

First, NL can resemble idiopathic perineuritis in the distribution of the cellular infiltrate, as in our published patient (figure in reference 3), in which there was a prominent perineurial involvement. Second, it may be erroneous to assume that the absence of systemic malignancy in life excludes NL in a given patient, as stated by the authors.¹ In fact, two patients with NL had peripheral neuropathy without systemic lymphoma clinically, including one with an occult retroperitoneal lymphoma, and one with lymphoma restricted to the nerves alone at autopsy.³

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Reply from the Authors: We were pleased to hear of two other cases of nonvasculitic mononeuritis multiplex, one almost exclusively sensory with perineuritis alone on biopsy, reported by Younger and Quan, and the other sensorimotor with peri- and endoneuritis, reported by Krendel and Costigan. Both patients were successfully treated with immunosuppressive therapy. The disorder is undoubtedly more common than is currently appreciated.

Both sets of authors draw on their previous experience and

writings to make the point that when confronted with such patients, it may be difficult to confidently exclude underlying systemic disease, such as NL and sarcoidosis. With respect to NL, one has at least the cellular infiltrate to scrutinize for histologic evidence of malignancy. As we said in our paper,¹ systemic disease is usually present in NL, and when apparently absent is another point, albeit not a foolproof one, against this diagnosis. We of course never said that absence of systemic lymphoma excludes NL. Whether cases of perineuritis with additional features such as anergy, for example, could be due to a limited form of sarcoidosis is an intriguing, but we think still speculative, idea. However, in the patients described in our paper in whom there were no major or minor features of sarcoidosis, the diagnosis of sarcoidosis cannot be made.

In any case, although the pathogenesis and natural history of perineuritis +/- endoneuritis is still unclear, we can agree that treatment of such patients with steroids, and presumably other immunosuppressive agents, often results in dramatic improvement and even complete remission.

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Seizures in the elderly

To the Editor: The frequency and pathogenesis of seizures in the elderly are yet to be clearly defined; 30% to 50% are due to stroke, but approximately 30% remain idiopathic.^{1,2} In this regard, the study by Ettinger and Shinnar³ on seizures in hospitalized elderly patients provides further perspective to similar community-based data. The authors use the International League Against Epilepsy guidelines for the classification of seizure types⁴ but, unfortunately, have also included syncopal convulsions as a cause of seizures. Henri Gastaut, in an elaborate series of experiments,⁵ demonstrated that syncope per se does not cause epileptic seizures. There is no evidence of EEG seizure activity during the convulsive event, only slow waves that may be interrupted by a period of "electro-cerebral silence" if the syncope is prolonged. Focal limb shaking during transient cerebral ischemia in patients with carotid stenosis is another similar occurrence that is occasionally misinterpreted as focal seizure activity. Again, the EEG demonstrates only focal slow-wave activity.⁶ Seizures in the context of cardiac arrest or shock have a more sinister etiology and may be due to possible cardioembolic stroke or ischemic encephalopathy.

As the authors note, the overestimation of generalized seizures in this population may represent seizures of "missed" focal onset. However, given this study's methodology, it may also be due to case selection bias in that patients were identified retrospectively by discharge diagnosis or by neurology service referral. Patients with generalized seizures attract the most attention and will therefore be seen preferentially. Those with postictal states (unwitnessed seizures), nocturnal seizures, absence status, or minor focal seizures often may be overlooked or misdiagnosed as other disorders (eg, confusional states, tremor).

It is interesting that, although over half the seizures were due to stroke, the predominant EEG pattern was epileptiform abnormalities. Previous studies, and the current multicenter "Seizures after stroke" study,⁷ have shown a correlation only to focal slow waves. This is probably due to white matter damage during the ischemic process, as proposed by Gloor et al.⁸

Ettinger and Shinnar also make reference to subcortical lacunar infarcts as a cause of seizures. These have been described previously but are uncommon. Although there is no cortical involvement on CT, such patients in fact have cortical deficits on ⁹⁹Tc HMPAO SPECT cerebral blood flow scans, accounting for the development of seizures.

Seizures in the elderly remain a poorly defined entity. Improvements in diagnosis and clinical definition of the dementias will further refine the one third of patients that remain cryptogenic. A properly controlled prospective study will then allow the true frequency and pathogenesis of this condition to be assessed.

Christopher F. Bladin, MD, FRACP
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Reply from the Authors: We thank Dr. Bladin for his comments and for the opportunity to reemphasize a few points.

We agree that certain types of seizures may be poorly recognized. Even though patients were prospectively identified for entry into our study, the failure of a clinician to identify a seizure would have prevented its inclusion into this series.

Although epileptiform abnormalities were highly represented in this population, we classified EEG findings according to the most salient abnormality, and, therefore, many cases with epileptiform features also had slow-wave abnormalities. The high incidence of epileptiform abnormalities may be explained by the substantial number of very ill patients, the evaluation of patients near the time of their acute-onset seizures, and the high number of acute destructive lesions often accompanied by periodic lateralized epileptiform discharges.

Dr. Bladin cites additional evidence of cortical deficits identified on ⁹⁹Tc HMPAO SPECT in patients with subcortical lacunar lesions. This supports our suggestion that lacunes are "indicative of more widespread cerebral vascular disease."³

We understand that the pathogenesis of convulsive syncope is controversial. We included these four cases because they presented as seizures rather than syncope. Excluding these few cases does not alter the results of the study. Cardiac arrest and shock can clearly cause seizures.

It must be recognized that there are significant differences between studies of hospitalized and community-based populations. In this series, the incidence of idiopathic seizures was low because of the high number of acute symptomatic etiologies for seizures and because hospitalization led to an intensive evaluation for each patient.

Seizures in the elderly are an important problem that deserves further investigation. We welcome further large-scale studies.

Alan B. Ettinger, MD
Stony Brook, NY

Shlomo Shinnar, MD, PhD
Bronx, NY

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Capsular warning syndrome

To the Editor: I very much appreciate the publication by Donnan et al¹ regarding the "capsular warning syndrome." This and other lacunar syndromes are particularly intriguing because they provide an opportunity for dynamic symptom observation and for therapeutic intervention—ie, they are not "completed" strokes. Such syndromes not only come and go as transient ischemic attacks, but they also may fluctuate with various levels of deficits or progress steadily or in a stuttering fashion. These phenomena support the concept of hypoperfusion in small-vessel stenosis.

I am not convinced that such syndromes are "therapeutically resistant." It may well be that attempted treatments have simply been inadequate. For example, Dobkin's "failure of heparin" was likely a consequence of blood pressure reduction prior to heparin treatment.² Although blood pressure reduction may have been advisable in order to reduce the possibility of hemorrhage, it may have reduced perfusion of the ischemic lesion, contributing to progression of the deficit. Similarly, hemodilution in various cases may have been too little, too late, or both. Certainly lacunar syndromes were never studied by subgroup analysis in the hemodilution trials.³⁻⁶

In my experience, blood pressure nonintervention with rapid hemodilution offers the best possibility of benefit, provided that hemiparesis has not progressed to hemiplegia before treatment is well under way.⁷ If blood pressure is reduced pharmacologically prior to completion of hemodilution, deficits tend to worsen immediately. If blood pressure is left untreated (no matter how high), it decreases spontaneously as a result of hemodilution.

Although I have used hetastarch for hemodilution, the case made by Goslinga et al⁶ for the use of albumin is well made on theoretical grounds and is supported by the clinical results of the Amsterdam Stroke Study for all strokes considered together.⁵

I heartily concur with the conclusion of Donnan et al about this syndrome being "ideal to test therapies," and I hope that further efforts can be dedicated to this end.

James L. Frey, MD
Phoenix, AZ

Reply from the Author: I would agree that the pathogenesis of the capsular warning syndrome most likely relates to critical hypoperfusion within single penetrating arteries. This is supported by the clinical pattern of presentation, namely, repetitive clinical episodes within a brief period of time. This temporal pattern is often seen in patients with critical stenoses of larger extra- or intracranial vessels. For this reason, blood pressure reduction at the time of presentation is likely, on theoretical grounds, to be unhelpful and to lead to an increased possibility of a fixed neurologic deficit developing. Allowing the blood pressure to settle spontaneously is therefore the most reasonable clinical approach.

As for the use of hemodiluting techniques, I would support Dr. Frey's contention that these need to be formally trialed in this clinical setting, as for other forms of transient cerebral ischemia. In previous studies⁴⁻⁶ specifically designed to test the hypothesis that early hemodilution may reduce subsequent morbidity and mortality, the therapeutic time windows used were too long to adequately exclude the null hypothesis. Except for the interesting report of Dr. Frey,⁷ hemodilution is untested in lacunar infarction. Formal randomized, controlled trials are needed to resolve this issue.

Geoffrey A. Donnan, MD
Melbourne, Australia

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Reaction times and L-dopa

To the Editor: Reaction-time data have yet to be analyzed in Quattrone and Zappia's investigation of oral pulse levodopa therapy (OPLT) in mild Parkinson's disease (PD).¹ These findings may bear on compensatory mechanisms¹ since a neurochemical model may underlie differences in reaction times (RTs) between extravertive and introverted premorbid personalities, the latter being a character type frequently reported in PD.^{2,3} This hypothesis is supported by compulsive ruminations preceding oculogyric crises linked to inefficient cortical circuits and dopamine (DA) abnormalities lateralized to the right hemisphere. The fact that delay-dependent speeding of RT, reflecting motor readiness, is abolished by depletion of DA^{4,5} suggests establishing the interdose interval in OPLT¹ by monitoring speech hesitation and switching pauses analyzed on a time-base by a microcomputer. Remote data acquisition is supported by participatory matching of pauses—a joint, mutually responsive rhythm⁵—and by the fact that the temporal dimension has a greater facilitating effect upon melody recognition than the melodic dimension does, once joint expectancies are generated.⁶

Ernest H. Friedman, MD
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Reply from the Authors: We appreciate the interest expressed in our paper by Dr. Friedman. The purpose of our study was to compare in mild PD the clinical effectiveness of OPLT, a new treatment modality, by comparing it with conventional multiple daily doses of levodopa. OPLT scheduled levodopa administration according to the duration of its clinical efficacy as determined by the modifications of movement time (MT), a reliable and objective indicator of clinical bradykinesia.⁷ Dr. Friedman suggests using RT to establish the interdose interval in OPLT by monitoring speech hesitation and switching pauses. This observation may be of interest, but it should be noted that RT and MT are often differentially impaired in PD⁸ and that levodopa replacement therapy may improve RT and MT in a quantitatively distinct fashion.⁹ It has been suggested that several factors, such as attentive,¹⁰ cognitive,⁸ and motor factors,¹¹ are involved in the delayed RT of PD patients, whereas only motor mechanisms are implicated in MT.¹² Moreover, in previous studies we demonstrated that MT was more correlated with bradykinesia than was RT⁷ and that, following levodopa

administration, the magnitude of MT improvement was related to PD severity, whereas RT improvement was not.¹³ These findings suggest that conclusions regarding MT abnormalities cannot be mutually applied to RT abnormalities in PD. MT, rather than RT, is an objective, simple, and reliable tool for evaluating bradykinesia and its levodopa-induced modifications in PD.

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Mario Zappia, MD
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Correction

In the September 1993 issue, the first letter in the Correspondence section (*Neurology* 1993;43:1858-1859) was mistitled. "Slowly progressive aphasia" should have read "Slowly progressive apraxia." Among the signatories, it is Dr. Jean-Claude Baron, not Dr. Jean-Louis Signoret, who is located in the city of Caen, in France. The editors apologize for the errors.

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Correction

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