Correspondence

Welding-related parkinsonism: Clinical features, treatment, and pathophysiology

To the Editor: We read with interest the case-control study in which Racette et al. compared the clinical features of welding-related parkinsonism and idiopathic PD.[1] They found that age at onset was much younger in welders and reached the conclusion that welding may be a risk factor for PD, possibly due to prolonged manganese exposure.[1] In the same issue of *Neurology*, this finding is discussed in an editorial.[2] Whereas the general principle that environmental factors may play a role in PD is accepted, the author points out that no exogenous agent has been consistently linked to PD. Welders are a relatively small group not comprising the whole of the PD patient population. Alternative strategies should be adopted to identify the environmental causes of PD—a task that is "akin to looking for needle in a haystack" in view of the large number of candidates.

Last year, *Neurology* published our larger case-control study of 990 patients with PD, in which the clinical features of patients with a history of exposure to hydrocarbons were compared to those of patients without such history.[3] The age at onset was younger in our study and led us to the same conclusion as that of Racette et al.; namely, that an environmental factor accelerates the onset of PD.

We also found that the disease was more severe throughout its course. This finding was not reported by Racette et al.[1] However, they compared the Hoehn & Yahr class as an index of severity, which is notoriously less sensitive than the methods we used—the Unified Parkinson's Disease Rating Scale (UPDRS) and the apomorphine test.

Hydrocarbons are commonly found in the environment, as they are constituents of varnish, glue, and many petroleum derivatives. Twenty percent of our patients had a history of exposure to these compounds, which usually occurred at their workplace. Welders are blue-collar workers, who are usually involved in a number of activities, not just welding, and may be exposed to a number of toxins besides manganese. We suggest that there may be a number of environmental factors that accelerate and worsen PD in genetically susceptible subjects, hydrocarbons being among the most frequent.

Maybe a few needles in the haystack have already been found.

G. Pezzoli and M. Canesi, *Milan, Italy*

To the Editor: We read with interest the article by Racette et al. on the clinical features of welding-related parkinsonism.[1] The authors compared the clinical features of 15 welders with parkinsonism to those of two control groups of patients with idiopathic PD. They found that the welders were younger at symptom onset but otherwise their clinical features were similar. Based on these findings, the authors suggest that welding may be a risk factor for PD that accelerates the onset of disease. Whereas this study represents a careful clinical description of a series of welders with parkinsonism, we differ with the authors in the interpretation of their results.

The authors describe their work as a case–control study. Racette et al. ascertained welders with parkinsonism and compared their concurrent clinical features to those of subjects with PD. This is more consistent with a cross-sectional design, as the disease state and factors of interest were ascertained simultaneously.[4] Cross-sectional studies are descriptive and therefore cannot be used to infer causation.

Welders were found to have a mean age at symptom onset of 46, 17 years younger than a control group of 100 consecutive PD patients drawn from their clinic. This striking result may be explained at least in part by factors other than exposure to welding. First, welders who had early onset of symptoms may have been preferentially referred because of concern about toxicity. The authors do not describe how these 15 cases were identified or if they attempted to identify other welding related cases in order to overcome this potential referral bias. Nor do the authors indicate if these welders are still working. Working subjects would likely be younger than a general PD population. Such selection bias may have drastically altered the results of this study. Second, it is not clear how the age at onset was determined or if the interviewers who obtained the history were blinded to the study hypothesis, raising the possibility of recall bias. In addition to these sources of bias, 53% of the welders had a positive family history (vs 32% of the sequential controls), arguing for an alternative mechanism for the earlier age at onset.

The data reported by Racette et al.[1] do not necessarily support any inference about welding as a risk factor in PD. A cohort study would be the best way to evaluate the role of welding in PD.

Bernard Ravina, MD, Andrew Siderowf, MD, John Farrar, MD, Howard Hurtig, MD, *Philadelphia, PA*

Reply from the Editorialist: I am grateful to Prof. Pezzoli for commenting on my editorial. Because the editorial space is limited, an exhaustive review of the literature was not possible. Pezzoli et al.[3] reported a large (990 patients) study, 20% of whom were exposed to hydrocarbons. These cases had an early onset and accelerated progression of parkinsonism.

A major objective of the analytic epidemiology of PD is to identify the cause. At times, an hypothesis is advanced that can only be verified by further epidemiologic studies as no laboratory investigations are possible. For example, in the early 1960s it was postulated that only those individuals who were exposed to von Economo encephalitis would develop PD and, therefore, the disorder would come to a natural end when all those at risk had died. Subsequent descriptive epidemiologic studies revealed no decline in the incidence to coincide with the decline in the von Economo exposed population. It was, therefore, concluded that von Economo encephalitis exposure was not the cause of idiopathic PD.

Where the hypothesis is not clearly defined and the studies are aimed at an environmental "search" for factors that may be associated with parkinsonism, the problem becomes more complex. Let us assume that all the idiopathic PD patients were consequent to one environmental cause. One could then compare the associated factors to multiple points on the circle where the cause would be the center of that circle. With the same center, many concentric circles can be drawn. Any point on any of those circles would have association with the center (cause). Because of the voluminous information such studies generate they are best suited to devise the next step—the more focused investigations. I made such a recommendation in the editorial. The paper by Racette et al.[1] was focused on individuals with one occupation. Prof. Pezzoli points out that these welders are "blue-collar" workers. Nonetheless, they share the same occupation and, as such, the same exposures, contrasted to the general population. Welders could be the subject of more targeted studies. For example, the trade unions could identify those who are entering the profession. Such individuals could then be followed clinically and with sequential PET scanning for evidence of PD. Racette et al.[1] could also conduct autopsy studies to determine the pathologic basis of parkinsonism in the patients they are following. In time, we would have the answer whether welding is related to PD.

The study by Pezzoli et al.[3] identified hydrocarbon exposure to seven different classes of chemicals and the patients were divided into more than nine occupations. Prof. Pezzoli has previously reported one patient with massive hydrocarbon exposure who had widespread pathology but no Lewy body inclusions. It is, however, conceivable that a low-level, long-term hydrocarbon exposure produces typical idiopathic PD. Pezzoli et al. have an excellent opportunity to answer that question. In that event they will have a better chance of success if they restrict the study to individuals involved in the same occupation and the same chemical exposure.

Ali H. Rajput, MD, FRCPC, *Saskatoon, Saskatchewan, Canada*

Reply from the Authors: We appreciate the comments from Pezzoli and Canesi and applaud their earlier work suggesting that hydrocarbon exposure may be one of a "number of environmental factors that accelerate and worsen PD . . ." In their study, Pezzoli et al. found a difference in age at onset (3 years; $p = 0.014$) between their "exposed" subjects and controls, and exposure to hydrocarbons correlated with disease severity ($r = 0.311$).[3] We

believe the 15-year difference in age at onset between welders and controls is a robust, clinically important finding ($p < 0.0001$). They criticize our study for use of an insensitive measure of disease severity, the Hoehn & Yahr scale. We agree that the Hoehn & Yahr scale is not a precise measure of disease severity. There is no gold standard for measuring disease severity. Ideally, one would like to count residual nigral dopaminergic cells. All clinical measures have serious limitations, including those used by Pezzoli et al. UPDRS motor scores when "on" reflect a large number of variables including timing of doses in relation to examination, variable dosing across patients, and potential confounds from drug-induced side effects such as dyskinesias. Their use of the apomorphine challenge is intriguing but it is not clear that it is any more accurate than the practical "off" score, which also has its limitations due to the long-duration motor benefits of levodopa.[5] It is possible that [^{18}F]FDOPA PET may prove to be a sensitive and accurate measure of disease severity and progression.[6,7] Finally, Pezzoli and Canesi accurately state that welders are exposed to a number of toxins; that is the reason we did not presume that manganese was the etiologic agent. As we stated in our paper,[1] "our findings do not prove that manganese is the toxic agent and other components of the fume could be responsible for parkinsonism in welders. Further studies are necessary to clarify this important issue. A detailed clinical evaluation of career welders compared to age-matched controls in a proper epidemiologic study will be essential to prove the relationship between welding and parkinsonism."

We also appreciate the interest in our manuscript of Ravina et al. Their first concern addresses the description of our study as a "case–control study." According to their reference,[4] a case–control study is "a case group or series of patients who have a disease of interest and a control, or comparison, group of individuals without the disease [which] are selected for investigation, and the proportions with the exposure of interest and the proportions from each group are compared." In a cross-sectional study, "the status of an individual with respect to the presence or absence of both exposure and disease is assessed at the same point in time." We agree that according to these definitions, our study more closely resembles a cross-sectional study. However, we believe that our study may be more accurately described as a "registry-based case-control study."[8] Nevertheless, "cross-sectional studies are, in general, useful for raising the question of the presence of an association rather than testing a hypothesis,"[4] which is consistent with our statement that "welding *may* be a risk factor for PD."[1] Although one may disagree about the best nomenclature for this study, their reference agrees with our interpretation.

Ravina et al. appropriately note potential biases in our study. They questioned our method of subject ascertainment. The subjects were consecutively ascertained "from a group of 953 new parkinsonian patients seen at our center between 1996 and 2000."[1] Referral bias for younger onset PD would likely affect all patients and not necessarily this selected group. If welders were preferentially concerned about employment status, we would expect that these patients would be employed at the time of referral. However, 12 of 15 patients had stopped working prior to their initial office visit. Patients' recall bias is unlikely as both groups had their initial office visits about the same time after their reported onset of symptoms. Investigator bias for age at onset is not relevant as these data were collected at the time of each patient's initial evaluation before we contemplated this study. As stated in the paper, all data were collected retrospectively. Finally, we agree that high frequency of positive family history in welders warrants additional studies to determine if there is a common genetic etiology in these subjects. Despite these limitations, we believe that our study provides suggestive data about the relationship between welding and PD, but as we stated in our article, a proper epidemiologic study will be necessary to prove this relationship.

Brad A. Racette, MD, *St. Louis, MO*

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Aboriginals with multiple sclerosis: HLA types and predominance of neuromyelitis optica

To the Editor: Mirsattari et al. address interesting points in their article on Canadian aboriginals with MS[1] but some aspects deserve discussion. The terms "Aboriginal" or "Aborigine" are often used to refer to native Australians, despite their broader meaning of original natives inhabiting an area. Most of the American continent uses the terms "Native American" or "Amerindian" when referring to indigenous people. As the authors point out, MS prevalence is higher among northern Europeans and Americans who claim that ancestry or have a predominantly Caucasian extraction than in Native Americans living in the same latitudes. Consensus from the Latin American Committee for Treatment and Research in Multiple Sclerosis (LACTRIMS)[2] and from an updated review on the status of MS in Latin America[3] suggests that non-mixed Native Americans or Amerindians are seldom affected by MS, whereas the prevalence continues to increase among Mestizos, who have a complex mixture of Caucasian and Mongoloid genetics and constitute the core of the Latin American population. Our review indicates that studies in the northern Mexican state of Chihuahua have failed to identify any MS cases in Tarahumara, Pima, Mazahua, and Quarijio Indian groups or those from the central areas of the country including Nahuatl, Mexicas, Huastecos, Otomies, and Purepecha, groups that are notable for migrating from their communities to the Mexico City area. The MS prevalence in the rest of the population in Mexico is estimated at 15/100,000. Approximately 7% of the 100 million Mexican population are non-mixed indigenous groups. No MS cases have been observed in northern Colombia (Kogis) and in other hemispheric native groups such Aymaras from Peru, Xingus, Yanomanis, and others from Brazil, and Mapuches from Chile.

It is possible that American Indians are protected against MS owing to their ancestral Asiatic genetics (Mongoloid), as apparently is also the case for their Canadian Aboriginal brothers (Algonkian) and Japanese cohorts. On the other hand, Mexican Mestizos with MS share HLA-DR2 and DR3 similar to European populations at high risk, a phenomenon suggesting that admixture between Caucasians and Amerindians is a recent event that has increased the risk of developing MS in the Mexican population and therefore in the rest of Latin America.[4] Colombian studies have also shown in local MS patients more frequency of HLA alleles DQ alpha 1.1, 1.2 with a significant low frequency of allele 3, similar to Caucasian populations residing in nontropical areas.[5]

Cooperative genetic, epidemiologic, and anthropological studies in native Americans and Asiatic people with MS may help to elucidate these questions.

Victor M. Rivera, MD, *Houston, TX;* and Jose A. Cabrera, MD, PhD, *Cienfuegos, Cuba*

Reply from the Authors: We thank Drs. Rivera and Cabrera for their interest in our manuscript. We disagree with their criticism of our use of the term "Aboriginal," preferring the terms "Native American" or "Amerindian" when referring to indigenous peoples. The terms preferred by indigenous peoples in Canada include "Aboriginals" or, alternatively, "First Nations." We chose the former term because it is clear to all readers and furthermore it is anthropologically precise, in contrast to "Native American" or "Amerindian," which are terms that are vague. The term "Aboriginal brothers" followed by Algonkian is also suggestive of pater-

nalism. The literature cited by Drs. Cabrera and Rivera is largely in abstract form with the exception of the paper by Alvarado–de la Barrera, which largely confirms our findings. We are pleased that our manuscript has generated some interest, but we would caution Drs. Cabrera and Rivera regarding their terminology with respect to indigenous peoples.

Seyed Mirsattari, MD, FRCP(C), *Manitoba, Winnipeg, Canada;* and Christopher Power, MD, FRCP(C), *Calgary, Alberta, Canada*

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Randomized controlled trial of IVIg in untreated chronic inflammatory demyelinating polyradiculoneuropathy

To the Editor: Mendell et al. report the results of a double-blind placebo-controlled randomized trial of IV immunoglobulin (IVIg) in patients with chronic inflammatory demyelinating polyneuropathy (CIDP).[1] I would question the need for such a trial given that prednisone, in a prospective randomized trial,[2] and plasmapheresis[3,4] and IVIg,[5,6] in prospective randomized controlled trials, have each previously been shown to be effective in the treatment of CIDP.

The authors cite a variety of reasons to justify their study. First, many patients enrolled in the prior studies of IVIg had previously received or were receiving other forms of immunomodulatory therapy and so it had not been unequivocally established that IVIg is effective in untreated CIDP. A second and related issue is the challenge from third-party carriers that the evidence does not support the use of IVIg as first-line therapy. Finally, the authors note that IVIg is not approved by the Food and Drug Administration for the treatment of CIDP. None of these factors mitigates the claim that there is general agreement among those who treat patients with CIDP that steroids, IVIg, and plasmapheresis are all effective forms of therapy.

It is widely acknowledged that clinical equipoise should serve as the moral underpinning of the randomized control trial (RCT).[7] Clinical equipoise reflects a collective professional uncertainty over the best treatment option. Whereas there is good evidence that prednisone, IVIg, and plasmapheresis may each benefit patients with CIDP, it could reasonably be argued that equipoise is present regarding which of these therapies is most effective. The need, therefore, is for a trial that will disturb the equipoise that exists. This would dictate that any further RCT compare two (or more) of the known effective therapies, rather than an already proven therapy with placebo.

Michael Benatar, *Boston, MA*

Reply from the Authors: We appreciate the comments of Dr. Benatar regarding our treatment trial of IVIg in CIDP. Clinical equipoise is an important issue that all investigators must consider in the design of any study. Dr. Benatar's concern that published reports of IVIg, steroids, and plasmapheresis precluded the need for our investigation of IVIg of previously untreated patients is flawed because the majority of CIDP patients in former studies were on maintenance therapy or had been treated and were drug-resistant. It is an erroneous assumption that the induction and maintenance response to treatment is the same in a chronic disorder or one altered by prior or ongoing therapy.[8-10] Our study was critical in order to test the hypothesis that IVIg is beneficial to the drug-naïve CIDP patient. It was gratifying to demonstrate a response as early as 10 days with continued improvement for the full length of the trial exceeding the number of estimated responders.[11]

Considering the extensive side effect profile of prednisone, the impediments to ongoing plasmapheresis including limited availability, indwelling lines, and need for immunosuppression to accompany ongoing treatment, and the occurrence of spontaneous improvement in some patients, the investigators and their respective institutional review boards believed that a genuine state of uncertainty regarding the merits of different therapies existed at the time of this study. We can now say with assurance that no patient should be refused IVIg as initial treatment if the patient's physician considers it the appropriate approach. We are indebted to Dr. Benatar for the opportunity to further emphasize the importance of our paper.

Jerry R. Mendell, *Columbus, OH*

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Vagus nerve stimulation and drug reduction

To the Editor: Tatum et al.[1] assessed drug reduction in 21 patients using vagus nerve stimulation (VNS) for a mean of 13.2 months. They fail to mention the stimulation parameters of the device. In addition, time of withdrawal of antiepileptic drugs (AED) or reduction of dose is unclear. Baseline seizure frequency of patients prior to implant of the stimulator was not assessed. There is no mention of decrease in seizure frequency at 3-, 6-, or 12-month intervals that led to AED withdrawal or dose reduction.

VNS is accepted as effective and safe for refractory partial epilepsy and possibly for refractory generalized epilepsy. The stimulation settings are not standardized and there is no consensus on output current settings or cycling paradigms. The output current is usually titrated to efficacy of treatment. It is unknown whether "more" or "less" current alters long-term outcome.

Stimulation parameters may have more impact on outcome than is known. Any information regarding the device settings is critical to better use of this device for treatment of epilepsy.

Vijay Venkataraman, MD, *Houston, TX*

Reply from the Authors: We thank Dr. Venkataraman for his comments on our article.[1] Our study included 42 patients with refractory epilepsy evaluated using an open-label design. Twenty-one patients had VNS implanted at our epilepsy center. These were then compared to retrospective case–matched control patients for analysis of drug reduction. Drug and dose reduction was

possible based upon each patient's seizure type(s) and frequency. Drug and dose taper schedules were individualized within the confines of routine clinical practice. Baseline seizure frequency was obtained 1 month prior to implantation for purposes of reporting outcome improvement. The small number of patients and heterogenous seizure types and frequencies were assessed for purposes of evaluating postimplantation percent seizure reduction. This is a similar format to outcome evaluations utilized with other postmarketing evaluation.[2]

Our follow-up of approximately 1 year (mean 13.2 months) was designed to approximate the greater efficacy of VNS previously noted in other open-label trials at the first year postimplant (relative to data available at 3 months). Our patient population was highly refractory with a mean duration of epilepsy of 17.0 years on a mean of 2.81 AED. As such, a longer period of approximately 1 year (or even longer) may better reflect an optimal time period to evaluate drug reduction relative to VNS efficacy.

We agree with the comments regarding device stimulus setting. Thus far, there have not been established, optimal generator parameters for individual patients. In our report, we note that a mean current of 1.85 mA was achieved. Furthermore, 42.9% of patients were maintained on duty cycles of <5 minutes. Most of the patients were maintained on parameters of 7 seconds "on" and 0.3 minutes "off." Whereas a "rapid cycling" paradigm has not yet been demonstrated to possess clear clinical advantage, this is one form of VNS that has previously received postmarketing attention.[5] Further studies may soon shed light on this very important clinical question for vagus nerve stimulation.

William O. Tatum, IV, DO, *Tampa, FL*

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Correction

In the article "Early development of intractable epilepsy in children: A prospective study" by Berg et al. (*Neurology* 2001;56:1445–1452), several errors appeared in the text. In the abstract, the parenthetical information in line 4 should read "(failure of ≥2 drugs, ≥1 seizure/month, over 18 months)." The first word of the second paragraph should be "Since." On page 1446, the first line of the third paragraph in Methods should read, "We defined intractability as failure, for lack of seizure control, of at least 2 first-line antiepileptic drugs (AED)[18] with an average of at least 1 seizure per month for 18 months and no more than 3 consecutive months seizure-free during that interval." The publisher apologizes for these errors.