

## Correspondence



## Preparedness for Bioterrorism?

*To the Editor:* Drs. Khan and Ashford, in their editorial (July 26 issue),<sup>1</sup> argue that the case of glanders in a microbiologist working in a military laboratory, reported by Srinivasan et al. in the same issue,<sup>2</sup> suggests the need for expanded preparedness for bioterrorism. We disagree. The lesson should instead be a warning that current “preparedness programs” are actually dangerous diversions of resources and that there is a need for primary prevention of all uses of biologic weapons. The microbiologist was not a victim of terrorism. He was an accidental casualty of the growing, multi-billion-dollar preparedness programs and of failure to include restrictions on hazardous research in the Biological Weapons Convention.

The deplorable lack of funding for public health programs increases the vulnerability of the United States and the world to outbreaks of infectious diseases, whatever their origin. But instead of making public health the priority, proponents of preparedness have embraced the idea of a “dual benefit” — a trickle-down theory suggesting that public health programs will gain from the allocation of billions of dollars for terrorism-preparedness programs dominated by military and police agencies. Drs. Khan and Ashford correctly distance themselves from the assertion of “intelligence sources” that a serious bioterrorism incident in the United States is inevitable. Even including the current anthrax scare, as of October 18, 2001, there had been one death and one hospitalization from the use of biologic weapons by terrorists, and there had been only a single incident of such use of chemical weapons. Nonetheless, the editorialists endorse preparedness programs without any evidence of their efficacy. Bioterrorism drills and stockpiles, and even the word “preparedness,” have been recycled from an earlier era of discredited “duck-and-cover” civil-defense drills and fallout shelters that were sold to a frightened public more than 40 years ago as preparedness for nuclear war.<sup>3</sup> Unlike bio-

terrorism, nuclear war and even biologic war may pose major risks, but secondary-prevention preparedness programs are ineffective responses that could also do considerable harm.

There are opportunity costs entailed in spending so many health dollars preparing for highly improbable events while real, natural epidemics threaten to overwhelm the world’s health resources.<sup>4</sup> Research on bioterrorism, such as the military research on glanders, may be interpreted by other nations as offensive-weapons development that could trigger a new arms race involving toxins and pathogens in the same way that attempted national missile-defense systems may cause renewed proliferation of nuclear missiles and warheads. Some former U.S. arms-control officials believe that recently revealed secret tests of a germ bomb by the Central Intelligence Agency and genetic engineering of more potent anthrax organisms by the Pentagon may violate the existing treaty on biologic warfare.<sup>5</sup> Subordinating health programs to military and police methods and priorities may also subvert public health.

Focusing on the treatment of casualties is also a problem, because it diverts attention from primary prevention. The same week that the article and editorial on glanders appeared in the *Journal*, an international agreement to strengthen the 1972 treaty banning biologic weapons was scuttled by the Bush administration “in order to protect military and trade secrets.”<sup>6</sup>

Preparedness for bioterrorism would neither have prevented the despicable terrorist attack on September 11, 2001, nor have reduced the terrible toll in deaths and destruction. It is a contradiction of good public health practice to spend billions of dollars for dubious and dangerous preparedness while blocking international efforts directed at the primary prevention of war and terrorism.

HILLEL W. COHEN, DR.P.H.

Albert Einstein College of Medicine  
Bronx, NY 10461  
hicohen@aecom.yu.edu

VICTOR W. SIDEL, M.D.

Montefiore Medical Center  
Bronx, NY 10467

ROBERT M. GOULD, M.D.

Santa Teresa Community Hospital  
San Jose, CA 95119

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## Treatment of Patients with Persistent Symptoms and a History of Lyme Disease

*To the Editor:* The study reported by Klempner et al. (July 12 issue)<sup>1</sup> showed that patients with chronic Lyme disease are ill; it also showed that the antibiotics used (intravenous ceftriaxone for one month, followed by oral doxycycline for two months) did not lead to improvement. The study did not answer the question of whether better outcomes would have resulted from a longer duration of either intravenous ceftriaxone or oral doxycycline therapy or from treatment with different antibiotics for the same or a longer period. The assumption that ceftriaxone and doxycycline are equivalent and additive treatments for chronic Lyme disease is untested. The mechanisms of action of the two drugs and their intracellular concentrations differ markedly.

Klempner et al. cite studies that my colleagues and I have performed with tetracycline<sup>2</sup> but do not discuss the pertinent observations — that tetracycline appears to be more effective than doxycycline, that intracellular-type antibiotics may be more effective than beta-lactams, and that the period of therapy required to achieve stable improvement is much longer than three months. We have since observed that other intracellular-type treatments appear to be effective for the treatment of chronic Lyme disease when they are used for longer periods.<sup>3</sup> There is a need to treat other chronic infections (e.g., tuberculosis, leprosy, Q fever, and hepatitis C) for more than three months.

The study by Klempner et al. was a beginning. What we need now, as the next step in finding successful treatments for all patients who are ill with chronic Lyme disease, is additional trials to evaluate alternative antibiotic therapies and different periods of treatment.

SAM T. DONTA, M.D.

Boston University Medical Center  
Boston, MA 02119  
sam.donta@bmc.org

1. Klempner MS, Hu LT, Evans J, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *N Engl J Med* 2001;345:85-92.
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*To the Editor:* The report by Klempner et al. raises an important question about a poorly understood condition: Does antibody-negative Lyme disease have a different response to treatment from that of antibody-positive disease? Although

no improvement was associated with antibiotic treatment among the seropositive patients, among those who were seronegative, the proportions of patients who had improvement in the physical and mental components of the 36-item Short-Form General Health Survey (SF-36) were larger in the antibiotic group (41 percent and 36 percent, respectively) than in the placebo group (22 percent and 26 percent, respectively).

In a 1996 report of a new polymerase-chain-reaction (PCR) technique, Mouritsen et al. noted that all nine samples that were positive for *Borrelia burgdorferi* DNA by PCR were from patients who were seronegative for antibodies to *B. burgdorferi*.<sup>1</sup> In the 29 samples from patients who were seropositive for antibodies, *B. burgdorferi* DNA was not detected. One reasonable explanation for this difference is that seronegative patients may have more difficulty clearing *B. burgdorferi* than patients with a robust antibody response.

MARK E. MCCAULLEY, M.D.

43480 RCR 36  
Steamboat Springs, CO 80487  
mccauley@springsips.com

1. Mouritsen CL, Wittwer CT, Litwin CM, et al. Polymerase chain reaction detection of Lyme disease: correlation with clinical manifestations and serologic responses. *Am J Clin Pathol* 1996;105:647-54.

*To the Editor:* The study by Klempner et al. appears to have been designed to fail. Why was a positive PCR test for *B. burgdorferi* a formal criterion for exclusion from a study intended to provide insight into the controversy over chronic Lyme disease? If there is a consensus that PCR positivity constitutes laboratory confirmation of active infection, and if patients with a positive result were excluded from this placebo-controlled study for ethical reasons, this point should have been emphasized.

Neuropsychiatric symptoms are a substantial part of chronic Lyme disease.<sup>1,2</sup> The neuropsychological scales used in the study were insufficient to assess the impairments in executive functioning and the psychiatric dysfunction that are seen in patients with persistent Lyme disease. The SF-36 is a subjective assessment scale, based on the patient's opinion, and there was a paucity of objective measures to assess the patient's status. Furthermore, at base line, the placebo and antibiotic groups appeared to have significantly different scores on the primary outcome measures. These observations suggest that randomization may have been inadequate, thereby invalidating the results of the study.

ROBERT BRANSFIELD, M.D.

Riverview Medical Center  
Red Bank, NJ 07701  
rbransfield@monmouth.com

STEPHEN BRAND, PH.D.

University of Rhode Island  
Kingston, RI 02881

VIRGINIA SHERR, M.D.

47 Crescent Dr.  
Holland, PA 18966-2105

1. Fallon BA, Nields JA. Lyme disease: a neuropsychiatric illness. *Am J Psychiatry* 1994;151:1571-83.
2. Bransfield RC. Diagnosis, treatment, and prevention of Lyme disease. *JAMA* 1998;280:1049.

*To the Editor:* Because Klempner and his colleagues used liberal enrollment criteria, it is likely that the groups they studied were rather heterogeneous. A more intensive analysis of subgroups might have revealed distinctive characteristics that could influence current medical practice or at least the design of future studies.

It is striking that the use of placebo was associated with demonstrable improvement in the mental component of the SF-36 score in 46 percent of seropositive subjects and that this was the highest favorable response rate in the study. Although the lack of an untreated control group in the study limits the interpretation of this observation, the possibility of a substantial placebo effect is not unimportant. These chronically ill patients may have benefited solely from the sustained interest and attention of the investigators. This study should serve not only to discourage the indiscriminate use of antibiotics in patients with persistent symptoms and a history of Lyme disease but also to encourage ongoing support of such patients. Having removed one thread of hope — that antibiotics would be helpful — the study should not become a justification for telling patients that there is currently nothing that can be done for them.

DAVID J. WYLER, M.D.  
194 Ward St.  
Newton Centre, MA 02459  
dwyler@mediaone.net

The authors reply:

*To the Editor:* Our study does indeed show that patients with persistent pain and neurocognitive symptoms after treatment for acute Lyme disease have substantial impairment of their quality of life. In contrast to Donta's interpretation that the patients did not have improvement, approximately one third of the patients treated with antibiotics had improved SF-36 scores and approximately one half had improved scores on the Fibromyalgia Impact Questionnaire. However, these results were not statistically different from those in the placebo group, suggesting that patients have symptoms that wane and wax spontaneously. In contrast to the findings in patients with the chronic infectious diseases that Donta cites as requiring prolonged therapy, we did not find evidence of persistent borrelial infection. Furthermore, when antibiotic therapy is given for tuberculosis, Q fever, or hepatitis C, objective responses are expected during the first three months of treatment. In contrast to Donta's uncontrolled studies, controlled trials of treatment for Lyme disease with the use of antibiotics that are excluded from the intracellular environment and those that are concentrated in the intracellular environment have had similar results.<sup>1-3</sup> Furthermore, *B. burgdorferi* appears mainly within tissues in extracellular sites.<sup>4</sup> Our studies suggest that trials of nonantibiotic therapies are warranted for this condition.

Contrary to McCauley's comments, there was no significant difference between the responses of the seronegative patients and those of the seropositive patients. At the baseline screening and during treatment, we also did not find

evidence of *B. burgdorferi* DNA in cerebrospinal fluid or blood samples from either the seronegative or the seropositive patients. We know of no evidence that in response to antibiotic treatment, seronegative patients "have more difficulty clearing *B. burgdorferi*" than do seropositive patients.

Bransfield et al. are correct that the detection of borrelial DNA by PCR in pretreatment blood and cerebrospinal fluid samples was a reason for excluding patients because such patients require antibiotic therapy. However, we screened over 1800 patients for this study, and no patient was excluded for this reason, since no patient was found to have a positive PCR assay or culture for borrelia — a result that confirms the absence of evidence of active infection in this clinical syndrome. We agree that the patients in our study exhibited neuropsychiatric symptoms in the absence of objective neurologic findings.<sup>5</sup> All patients were given an extensive battery of neurocognitive tests in addition to the SF-36. A forthcoming analysis of these data should be sufficient to demonstrate any cognitive impairment, should it exist. The randomization protocol was adequate, since baseline values for the primary outcome measures in all patients were statistically equivalent in the placebo and antibiotic groups.<sup>6</sup> Moreover, each patient served as his or her own control, since the clinical response was measured by calculating a change in health status for each patient.

Contrary to Wyler's comments, our criteria for enrollment were very stringent. Less than 10 percent of screened subjects actually qualified for the study. We agree that antibiotic therapy offers no long-term benefit, and further studies on pathogenesis and treatment are needed.

ARTHUR WEINSTEIN, M.D.  
Washington Hospital Center  
Washington, DC 20010

MARK S. KLEMPNER, M.D.  
Boston University School of Medicine  
Boston, MA 02118

1. Dattwyler RJ, Volkman DJ, Conaty SM, Platkin SP, Luft BJ. Amoxicillin plus probenecid versus doxycycline for treatment of erythema migrans borreliosis. *Lancet* 1990;336:1404-6.
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## Hepatitis C Virus Infection

*To the Editor:* In their article on hepatitis C virus (HCV) infection (July 5 issue),<sup>1</sup> Lauer and Walker note that the pegylated interferon peginterferon alfa-2a has been approved by the Food and Drug Administration (FDA), when in fact it is peginterferon alfa-2b that has received FDA approval. Large studies in the United States and Europe of the use of either brand of pegylated interferon plus ribavirin have been completed and found sustained virologic response rates of

56 percent and 61 percent.<sup>2,3</sup> The combination of peginterferon alfa-2b plus ribavirin has been approved in Europe and is expected to be approved soon in the United States.

The comments about the lack of value of retreatment in patients with no response to interferon monotherapy are inaccurate; numerous studies have found sustained virologic response rates of 20 to 30 percent among such patients.<sup>4</sup> Approximately 30 percent of patients with chronic HCV infection have normal alanine aminotransferase levels.<sup>4,5</sup> Studies have shown that the sustained virologic response rates for either interferon monotherapy or combination therapy are equivalent to those among patients with elevated alanine aminotransferase levels. Although it is recognized that cirrhosis develops in only a small percentage of patients with normal alanine aminotransferase levels, as many as 20 percent of such patients will have stage 3 or stage 4 fibrosis. It is important to direct therapy to prevent progressive liver disease, but given the improvements in antiviral therapy and the opportunity to eradicate virus in an increasing number of patients, most hepatologists believe that patients with mild disease should also be treated.

BRUCE R. BACON, M.D.  
ADRIAN M. DI BISCEGLIE, M.D.  
Saint Louis University  
St. Louis, MO 63110-0250  
baconbr@slu.edu

*Editor's note:* Drs. Bacon and Di Bisceglie receive research support from and have consulting relationships with Schering-Plough and Roche Laboratories.

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*To the Editor:* Lauer and Walker did not answer the following question: Do persons with HCV infection and normal liver-function results need a liver biopsy?

JAMES R. KORB, M.D.  
Southern California Permanente Medical Group  
Los Angeles, CA 90034  
james.r.korb@kp.org

*To the Editor:* Drs. Lauer and Walker overestimate the importance of HCV as a cause of chronic liver disease by concentrating on review articles, consensus statements, and retrospective studies while ignoring the prospective studies. Currently there are four large, long-term, retrospective-prospective studies involving patients who have received trans-

fusions. These studies demonstrate a rather favorable outcome of HCV-associated liver disease.<sup>1-4</sup> In contrast to the consensus statement the authors cite indicating that liver cirrhosis develops in 20 to 30 percent of patients with HCV, much lower rates of cirrhosis have been documented in the four prospective studies.<sup>1-4</sup>

HANS L. TILLMANN, M.D.  
Stolze Str. 41  
30171 Hannover, Germany  
hansstillmann@web.de

1. Kenny-Walsh E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. *N Engl J Med* 1999;340:1228-33.
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*To the Editor:* Drs. Lauer and Walker do not discuss the association between HCV infection and diabetes mellitus. This association was described in 1995 and has been supported by more recent cross-sectional studies in which patients with HCV infection were matched according to age, sex, and severity of cirrhosis. In one study, the prevalence of diabetes mellitus was 23.6 percent among patients with HCV infection but 9.4 percent among those infected with hepatitis B virus, and the prevalence was associated with the Child-Pugh score among patients with cirrhosis.<sup>1</sup> A similar prevalence has been found in other studies and in the experience at our institution.<sup>2</sup> Persons older than 40 years of age with HCV infection have a risk of diabetes that is three times that of those without HCV infection.<sup>3</sup> Furthermore, HCV-related cirrhosis was found to be a predictor of the development of diabetes after liver transplantation.<sup>2</sup>

KEVAN C. HEROLD, M.D.  
Columbia University  
New York, NY 10032  
kh318@columbia.edu

1. Caronia S, Taylor K, Pagliaro L, et al. Further evidence for an association between non-insulin-dependent diabetes mellitus and chronic hepatitis C virus infection. *Hepatology* 1999;30:1059-63.
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*To the Editor:* Lauer and Walker report that current psychosis or a history of psychosis is an absolute contraindication to treatment with interferon alfa and ribavirin in persons who are infected with HCV. To support this conclusion, the authors cite the consensus statement on hepatitis C from the European Association for the Study of the Liver.<sup>1</sup> Yet a clear justification for such a conclusion is lacking. The 1997 consensus statement from the National Institutes of Health on the management of hepatitis C<sup>2</sup> does not include psychosis

as a contraindication to treatment with interferon alfa. In fact, a survey of 11,241 patients with chronic viral hepatitis treated with interferon alfa reported only 10 adverse events relating to psychosis.<sup>3</sup> None of these events were considered life-threatening, and all remitted with the discontinuation of interferon or with treatment with appropriate psychiatric medication.

SETH HIMELHOCH, M.D.  
Johns Hopkins University  
Baltimore, MD 21287-6220  
shimelh1@jhmi.edu

1. EASL International Consensus Conference on Hepatitis C: Paris, 26-28, February 1999, consensus statement. *J Hepatol* 1999;30:956-61.
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*To the Editor:* The review on HCV infection indicates that hemoglobinopathies are considered absolute contraindications to treatment with ribavirin. We think that patients with hemoglobinopathies can tolerate ribavirin, but they require close monitoring.

Hemoglobinopathies are the most common autosomal recessive diseases. The high prevalence of positivity for HCV antibodies among patients with hemoglobinopathies is related to increased requirements for blood transfusion,<sup>1</sup> and the increased iron stores might accelerate the progression of the disease. Therefore, antiviral therapy in patients with HCV infection and concomitant hemoglobinopathy is warranted.

A study from the United Kingdom demonstrated the feasibility of combination therapy with interferon and ribavirin in patients with thalassemia.<sup>2</sup> Five of 11 patients had a sustained virologic response. Transfusion requirements were increased during therapy. We also successfully treated two patients with  $\beta$ -thalassemia; both had a sustained virologic response. With regard to antiviral treatment in patients with HCV infection and sickle cell disease, a single successful case report is available.<sup>3</sup> Thus, interferon and ribavirin therapy appears feasible and should be considered in patients with HCV infection and hemoglobinopathy.

ROBERT J. DE KNEGT, M.D.  
ARIE P. VAN DEN BERG, M.D.  
Groningen University Hospital  
9700 RB Groningen, the Netherlands  
r.j.de.knegt@int.azg.nl

1. Erer B, Angelucci E, Lucarelli G, et al. Hepatitis C virus infection in thalassemia patients undergoing allogeneic bone marrow transplantation. *Bone Marrow Transplant* 1994;14:369-72.
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terferon alpha and ribavirin for chronic hepatitis C virus infection in thalassemic patients. *Br J Haematol* 1997;98:850-5.

*To the Editor:* In the article on HCV infection, hepatitis A vaccine is incorrectly described as a recombinant vaccine. Both hepatitis A vaccines licensed by the FDA and available in the United States are inactivated vaccines, prepared by propagating cell-culture-adapted virus in human fibroblasts and inactivating the purified product with formalin.<sup>1,2</sup> To my knowledge, there are no recombinant hepatitis A vaccines available anywhere in the world.

BETH P. BELL, M.D., M.P.H.  
Centers for Disease Control and Prevention  
Atlanta, GA 30333

1. Peetermans J. Production, quality control and characterization of an inactivated hepatitis A vaccine. *Vaccine* 1992;10:Suppl 1:S99-S101.
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The authors reply:

*To the Editor:* We agree with Bacon and Di Bisceglie that preliminary abstracts of studies in which pegylated interferons plus ribavirin are being used are promising, but final recommendations should await peer review. We also agree that their own study revealed relatively good results (a sustained virological response rate of 30 percent) after retreatment in patients who had no response to interferon. However, three other studies<sup>1-3</sup> have shown a sustained virologic response to combination therapy in only 4 to 14 percent of patients who previously had no response to interferon alone.

The issue of which patients require a biopsy was raised by Korb, and the question of whom to treat was raised by Bacon and Di Bisceglie. We recommend a liver biopsy for patients with viremia who have persistently normal aminotransferase levels, since the results of a biopsy can greatly influence decisions regarding treatment. We recommend treatment for those with a biopsy specimen showing liver disease,<sup>4</sup> but we believe that close observation is an option that can be discussed with those whose biopsy specimens show very mild disease activity. We do not recommend therapy outside of controlled clinical trials for patients with viremia who have normal liver-function results and normal liver histology.

In response to Tillmann: we indeed discussed prospective studies and their limitations in the review. We did not state that cirrhosis develops in 20 to 30 percent of patients; the numbers we gave were 15 to 20 percent. These are still estimates but are in agreement with more recent reports.<sup>5</sup>

We appreciate the comments by Herold about the possible association of HCV infection with diabetes mellitus. Because of space limitations, we were not able to discuss this interesting issue.

We agree with Himelhoch and de Knegt and van den Berg that some contraindications to interferon and ribavirin should be addressed again in the future, especially since groups of patients that are currently excluded from therapy may have a high prevalence of HCV infection. Our review was intended for a general audience, and pending additional studies, we would not recommend treating patients with a

history of psychosis or with hemoglobinopathies except in specialized centers.

We apologize for the errors that were noted. Indeed, peginterferon alfa-2b, not peginterferon alfa-2a, has been approved by the FDA. Although the dose of ribavirin must be reduced for a substantial number of patients, less than 1 percent, not 20 percent, have to discontinue ribavirin therapy because of drug-induced anemia. As Bell correctly notes, hepatitis A vaccine is an inactivated vaccine.

BRUCE D. WALKER, M.D.

GEORG M. LAUER, M.D.

Massachusetts General Hospital  
Charlestown, MA 02129-2000  
bwalker@helix.mgh.harvard.edu

1. Cavalletto L, Chemello L, Donada C, et al. The pattern of response to interferon alpha (alpha-IFN) predicts sustained response to a 6-month alpha-IFN and ribavirin retreatment for chronic hepatitis C. *J Hepatol* 2000; 33:128-34.
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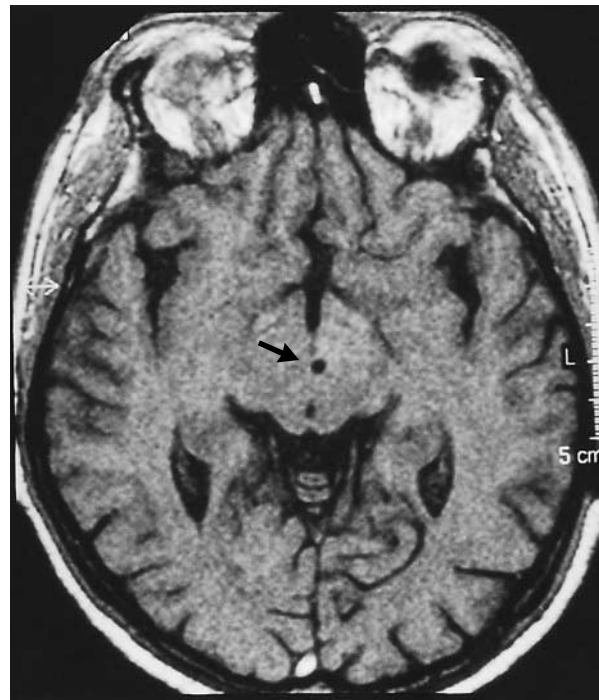
### Stereotactic Stimulation of Posterior Hypothalamic Gray Matter in a Patient with Intractable Cluster Headache

*To the Editor:* Cluster headache is the most severe form of primary headache.<sup>1</sup> Positron-emission tomography has shown activation of the homolateral posterior inferior hypothalamic gray matter during attacks of cluster headaches, a finding that is apparently specific to the condition.<sup>2,3</sup> and voxel-based morphometric magnetic resonance imaging (MRI) has documented alteration of the same area,<sup>4</sup> suggesting that cluster headache may be initiated in this area. We reasoned that stereotactic stimulation of this area might prevent activation and relieve intractable forms of cluster headache.

We report on a 39-year-old, right-handed man who had excruciatingly painful daily cluster headaches for five years. The attacks lasted between 30 minutes and 4 hours, occurred two to five times a day, and were associated with striking oculofacial swelling. Ninety percent were on the right side, and the remainder were on the left; they were never bilateral.<sup>5</sup> Extensive investigation including cerebral MRI, magnetic resonance angiography, and catheter angiography excluded other conditions.<sup>5</sup> No drugs produced worthwhile benefit.<sup>5</sup> After a second percutaneous thermal rhizotomy, the right-sided headaches disappeared. Unfortunately, from that moment, the left-sided attacks worsened to mirror exactly those that had previously occurred on the right side. Left trigeminal surgery was contraindicated by the risk of corneal sequelae, which could have left the patient totally

blind (he was blind in the right eye as a result of a hemorrhage in the vitreous humor).

We proposed the stereotactic implantation of an electrode, targeting the posterior inferior homolateral hypothalamic gray matter.<sup>2-4</sup> After informed consent was obtained, the operation was performed with the patient under local anesthesia. The electrode (model 3089, Medtronic, Minneapolis) was inserted 6 mm posterior to the midpoint between the anterior and posterior commissures, 2 mm left of the mid-



**Figure 1.** Axial T<sub>1</sub>-Weighted Postoperative Magnetic Resonance Image Showing the Electrode (Arrow) within the Posterior Inferior Left Hypothalamus.

line, and 8 mm below the commissural plane.<sup>2-4</sup> Intraoperative electrical stimulation induced no side effects. The permanent generator (Solettra, Medtronic), embedded in a subclavicular pocket, was connected through a subcutaneous tunnel.

Therapeutic stimulation was continuous and unipolar. The position of the permanent electrode was verified by postoperative MRI (Fig. 1). When stimulation was provided at a frequency of 180 Hz, a voltage of 3 V, and a pulse width of 60  $\mu$ sec, the attacks disappeared after 48 hours. Twice, without the patient's being aware of it, the stimulator was switched off and the left-sided attacks reappeared 48 hours later. When the stimulator was turned on again, the attacks disappeared 48 hours later. Thirteen months after the operation, the patient remains free of pain. The

precision and safety of this method suggest that it should be tried in other patients with intractable chronic cluster headaches.

MASSIMO LEONE, M.D.  
ANGELO FRANZINI, M.D.  
GENNARO BUSSONE, M.D.

Carlo Besta Neurological Institute  
20133 Milan, Italy  
bussone@istituto-besta.it

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