study was closed to the accrual of patients, there was a 100 percent increase in median survival for patients who received chemotherapy ($P = 0.0008$). This value had crossed the truncated O'Brien–Fleming group sequential boundary,* suggesting clear statistical evidence of a treatment difference and serving as the statistical basis for study closure.

In any clinical trial subject to random error, there is still a 5 percent chance of finding a difference between two treatments when in fact none exists. This would apply to a trial that continued to completion, regardless of size, as well as to one that was closed early on the basis of group sequential methods. This is the rationale for confirmatory studies such as those currently under way to retest the findings of our recent Cancer and Leukemia Group B trials.

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*O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979; 35:549-56.

CHRONIC NEUROLOGIC MANIFESTATIONS OF LYME DISEASE

To the Editor: In our opinion, the data provided by Logigian and coworkers (Nov. 22 issue)* are not sufficient to prove that chronic disease of the central nervous system was caused by *Borrelia burgdorferi*. Our main criticism concerns the interpretation of the cerebrospinal fluid (CSF):serum ratio of specific antibodies. If total IgG and specific antibodies could be measured with absolute accuracy, the ratio should have a value of 1 in all patients without a central-nervous-system immune response. If the accuracy is lower, as in practice it always will be, a logarithmic gaussian distribution with a mean value of 1 has to be expected. In the absence of normal values, the cut-off values should be defined on the basis of statistical considerations. Because values below 1 can only be interpreted by statistical dispersion, the cut-off for positivity should be drawn at the reciprocal of the lowest value measured. Since Logigian et al. found values as low as 0.5, only ratios higher than 2.0 can be considered definitely positive.

Because the study lacks case controls or a population-based estimate of incidence, the possibility cannot be excluded that the neurologic disease represented the accidental coincidence of a history of Lyme disease with another disease. Even if the neurologic disease was caused by *B. burgdorferi*, a partial recovery from the acute disease seems more probable than progressive disease. In two of our patients reporting similar symptoms after Lyme disease, antibiotic therapy seemed to improve some of the symptoms, even though objective improvement could not be documented. During a follow-up period of one year, the patients presented with the same symptoms again, although the clinical findings did not change at all. We believe that the importance of chronic neuroborreliosis is overestimated.

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*Logigian EL, Kaplan RF, Steere AC. Chronic neurologic manifestations of Lyme disease. N Engl J Med 1990; 323:1438-44.

The above letter was referred to the authors of the article in question, who offer the following reply:

To the Editor: In diagnosing infection of the central nervous system in Lyme borreliosis, Drs. Stark and Wurster question the validity of a cut-off value of 1 for the CSF:serum ratio of antibody to *B. burgdorferi*. We have published a separate study on the evaluation of the intrathecal antibody response to *B. burgdorferi* in 37 American and 30 German patients with Lyme borreliosis and in 12 control subjects.[1] The antibody responses were determined by capture enzyme immunoassay, which measures directly the proportion of specific to total antibody. Unlike the indirect systems commonly used, this method does not require the adjustment of serum and CSF concentrations in order to compare specific antibody titers.

In that study, American patients with neuroborreliosis had significantly lower CSF:serum ratios of antibody to *B. burgdorferi* than German patients. Even among the patients with meningitis, which is known to be caused by intrathecal infection with the spirochete, the mean CSF:serum ratio of specific IgG antibody to the spirochete was 17 in the European patients as compared with 2 in the American patients ($P<0.05$). Of 12 American patients with chronic encephalopathy, only 5 (42 percent) had CSF:serum ratios above 1 but not usually more than 2. In comparison, 6 seropositive patients with peripheral neuropathy due to Lyme disease and 6 seropositive patients with chronic fatigue after Lyme disease had a mean ratio of 0.7 (range, 0.3 to 1), and none of the 12 patients with other inflammatory neurologic diseases had a ratio above 1. Thus, the mean values among patients with Lyme disease who did not have central nervous system abnormalities were not normally distributed around 1, as hypothesized by Drs. Stark and Wurster.

For a number of reasons, only one of which concerns the central nervous system immune response, we believe that the 27 patients described in our recent article in the *Journal* had chronic neurologic manifestations due to Lyme disease.[2] Most of the patients had symptoms of both an encephalopathy and a polyneuropathy, manifested primarily by memory impairment, distal paresthesias, or radicular pain. In most instances, memory impairment could be demonstrated on neuropsychological tests, total protein levels in CSF were elevated, and electromyograms showed evidence of an axonal polyneuropathy. Although all the patients had current evidence of immunity to *B. burgdorferi*, only about half of those with encephalopathy had CSF:serum ratios of IgG antibody to the spirochete between 1 and 2.

Determination of the intrathecal antibody response to *B. burgdorferi* has limitations as a diagnostic test. First, demonstration of an intrathecal antibody response is an inconsistent finding among our patients with central nervous system abnormalities. Perhaps in some patients with this systemic illness, more antibody is produced in peripheral lymph nodes than in the central nervous system, and therefore selective concentration of specific antibody cannot be demonstrated in CSF. Second, we agree that a positive test does not prove the presence of a live spirochete; selective concentration of specific antibody in CSF may still be found for at least months, albeit at lower levels, in patients who have apparently been treated successfully for neuroborreliosis.[2] We do not think, however, that this is the explanation for the elevated CSF:serum ratios in our patients with encephalopathy, since elevated ratios were not found more frequently in the subgroup of these patients who had previously had early neurologic manifestations of the illness.

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1. Steere AC, Berardi VP, Weeks KE, Logigian EL, Ackerman R. Evaluation of the intrathecal antibody response to *Borrelia burgdorferi* as a diagnostic test for Lyme neuroborreliosis. J Infect Dis 1990; 161:1203-9.
2. Logigian EL, Kaplan RF, Steere AC. Chronic neurologic manifestations of Lyme disease. N Engl J Med 1990; 323:1438-44.

TOTAL RECOVERY OF VISUAL FUNCTION AFTER TREATMENT FOR CEREBRAL CYSTICERCOSIS

To the Editor: Brain cysticercosis is now treated effectively with either albendazole or praziquantel,[1,2] but most studies demonstrating the efficacy of cysticidal drugs have been based on objective evidence from imaging studies of the disappearance of cysts after cysticidal therapy. Even with this evidence, some authors have doubts about the real benefits of cysticidal therapy when weighed against the possibility of adverse reactions in the host due to the acute inflammation triggered by the destruction of the parasites.[3]

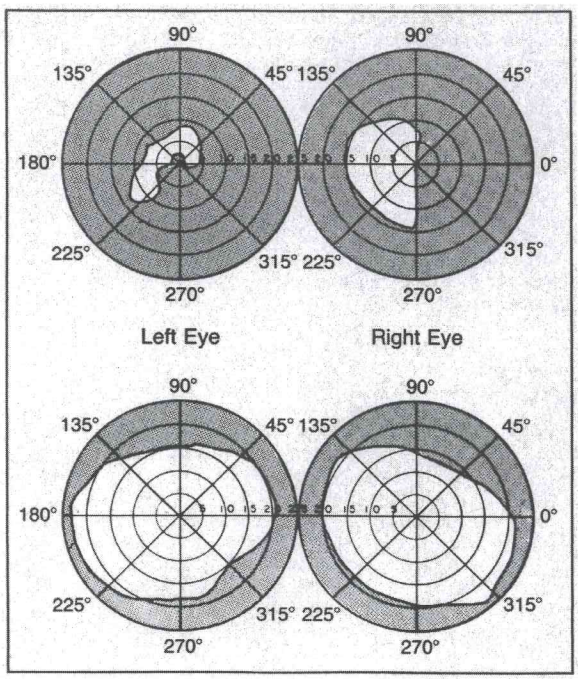

Figure 1. Bilateral Campimetry before (Upper Panel) and after (Lower Panel) Eight Days of Albendazole Therapy, in a Patient with Cysticercosis.

Note the full recovery of visual fields.

We present evidence of the total recovery of a neurologic function immediately after therapy with albendazole. A 43-year-old woman started to have diminution of visual acuity 10 months before consultation. The deficit progressed, and by the time of admission she had severe difficulty identifying nearby objects. On ophthalmologic examination, she could distinguish objects only at 30 cm with the left eye, her visual acuity was 20/25 with the right eye, and both visual fields were diminished concentrically (Fig. 1). The rest of the neurologic examination was normal. Magnetic resonance imaging demonstrated three large cysticerci at the base of the brain (Fig. 2). Analysis of the cerebrospinal fluid showed normal pressure, a protein level of 26 mg per deciliter, a count of 12 mononuclear cells per cubic millimeter, and a complement-fixation test and enzyme-linked immunosorbent assay positive for cysticercosis. After a heated discussion about the therapeutic approach, in which opinions were divided about the advantages of surgery or drug therapy, the latter was chosen, and therapy with albendazole (15 mg per kilogram of body weight daily for eight days) was started. In addition, dexamethasone (8 mg every eight hours) was administered intravenously. The patient reported no symptoms during treatment and had a notable improvement of visual function a few days after the beginning of therapy. On ophthalmologic examination at the end of treatment, her bilateral visual acuity was 20/20 with normal visual fields (Fig. 1), and magnetic resonance imaging documented the successful destruction of cysticerci (Fig. 2). The patient was discharged with a therapeutic regimen of 50 mg of prednisone every other day for three months.

This case documents a striking recovery of neurologic function immediately after cysticidal therapy, with successful destruction of subarachnoid cysticerci. Because of the location of the lesions and the severe damage to the patient's vision, the fear of complications of drug therapy, with the possibility of a worsening of valuable neurologic function, made the therapeutic decision difficult. However, the recent finding that the simultaneous administration of albendazole and dexamethasone increases the plasma levels of

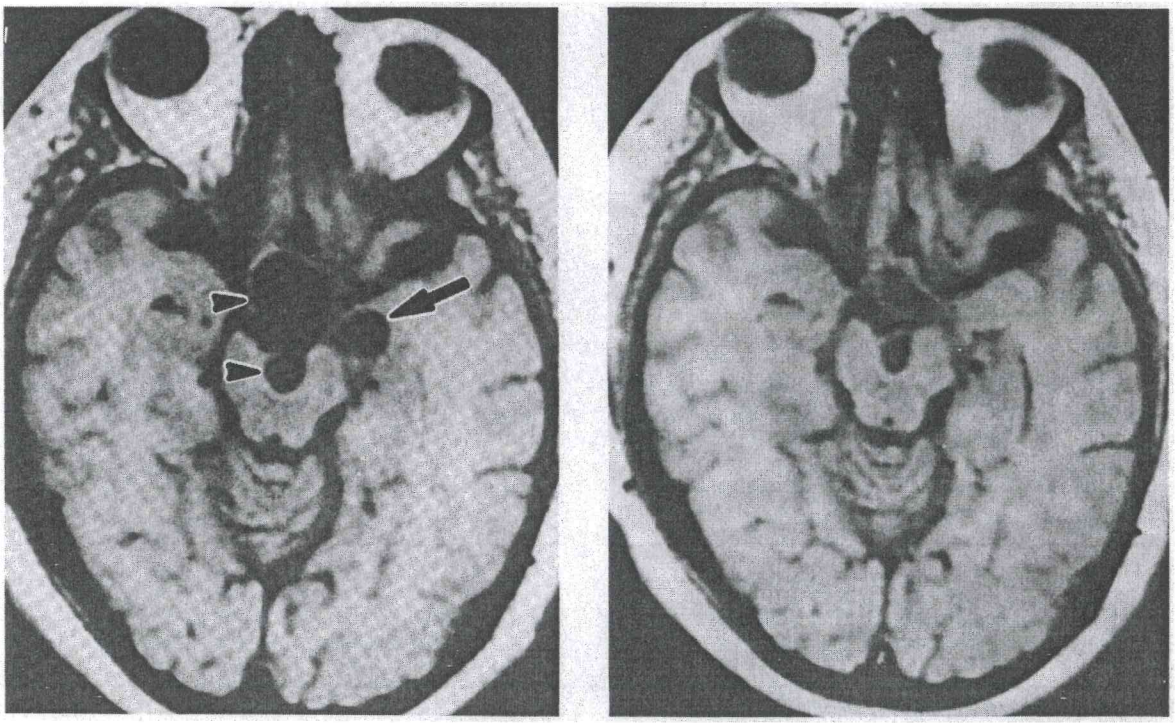

Figure 2. Magnetic Resonance Image of the Base of the Brain before (Left Panel) and after (Right Panel) Eight Days of Albendazole Treatment.

Three arachnoid cysticerci are visible before treatment, two in the parasellar region (arrowheads) and one compressing the left temporal amygdala (arrow). All lesions disappeared by the end of treatment.

albendazole[4] prompted us to decide on drug therapy instead of surgery.

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1. Sotelo J, Escobedo F, Rodriguez-Carbajal J, Torres B, Rubio-Donnadieu F. Therapy of parenchymal brain cysticercosis with praziquantel. N Engl J Med 1984; 310:1001-7.
2. Sotelo J, del Brutto OH, Penagos P, et al. Comparison of therapeutic regimen of anticysticercal drugs for parenchymal brain cysticercosis. J Neurol 1990; 237:69-72.
3. Moodley M, Moosa A. Treatment of neurocysticercosis: is praziquantel the new hope? Lancet 1989; 1:262-3.
4. Jung H, Hurtado M, Medina MT, Sanchez M, Sotelo J. Dexamethasone increases plasma levels of albendazole. J Neurol 1990; 237:279-80.

ACQUIRED FACTOR VIII DEFICIENCY AND POLYRADICULONEUROPATHY

To the Editor: A 77-year-old man was hospitalized with a two-month history of progressive weakness in all four extremities. Electromyography and studies of nerve-conduction velocity revealed acute denervation consistent with acute idiopathic polyradiculoneuropathy, a condition resembling the Guillain–Barré syndrome. During the hospitalization, a coagulopathy developed, manifested by purpuric lesions and abnormal prothrombin and partial-thromboplastin times. Laboratory analysis revealed a delayed inhibitor to factor VIII. Corticosteroid therapy was begun in an attempt to suppress production of the inhibitor. After 10 days of therapy, there was no change in the abnormal coagulation-test results, and a large retroperitoneal hematoma developed spontaneously. Therapy was begun with factor VIII concentrate followed by cyclophosphamide, vincristine, and prednisone, as described by Lian et al.[1] Shortly after receiving the first course, the patient died of aspiration pneumonia.

Factor VIII inhibitors have been described in association with autoimmune-related disorders, such as rheumatoid arthritis and systemic lupus erythematosus.[2] Berger et al.[3] first reported the coexistence of such an inhibitor in a patient with chronic inflammatory polyradiculoneuropathy. This neuropathy is a variant of Guillain–Barré syndrome, which is thought to be mediated by an autoimmune response to Schwann cells and myelin. The case we observed showed a similar association between a polyradiculoneuropathy and a coagulopathy, both presumed to be due to the production of acquired antibodies and thus offering further support for the presence of an acquired defect in immune regulation that accounts for these coexistent pathologic phenomena.

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1. Lian EC-Y, Larcada AF, Chiu AY-Z. Combination immunosuppressive therapy after factor VIII infusion for acquired factor VIII inhibitor. Ann Intern Med 1989; 110:774-8.
2. Green D, Lechner K. A survey of 215 non-hemophilic patients with inhibitors to factor VIII. Thromb Haemost 1981; 45:200-3.
3. Berger JR, Rosenfeld WE, Sheremata WA, et al. Chronic inflammatory polyradiculoneuropathy complicated by factor VIII antibody. Neurology 1983; 33:1224-6.

INCREASED PLASMA ENDOTHELIN LEVELS IN PATIENTS WITH RAYNAUD'S PHENOMENON

To the Editor: The pathogenesis of Raynaud's phenomenon is still unclear. Many factors, including abnormal platelet aggregation and serotonin hypersensitivity, have been postulated to contribute to the pathogenesis of Raynaud's vasospasm,[1] but the precise mechanism remains unknown.

Endothelin, a novel endothelium-derived peptide with a potent and sustained constrictive effect on a variety of blood vessels,[2] has been suggested to play a part as a vasoactive hormone in the regulation of vascular resistance and blood-flow distribution. To elucidate whether human endothelin is involved in Raynaud's phenomenon, we measured the levels of endothelin in plasma from patients with this disorder. Fourteen patients (13 women and 1 man, 19 to 60 years of age), 7 with primary Raynaud's phenomenon and 7 with Raynaud's phenomenon secondary to systemic sclerosis, were studied. The diagnosis was based on accepted criteria.[3,4] Nine healthy volunteers, matched for age and sex, served as controls. Blood was collected from an antecubital vein after the patients had been recumbent for at least 30 minutes. Plasma, assessed by an investigator who did not know the patients' diagnoses, was injected into prepared Bond Elut C_{18} solid-phase cartridges (Analytichem International), washed with 4 ml of methanol and deionized water, and eluted with 2 ml of 90 percent methanol/1 percent trifluoracetic acid. Eluted samples were concentrated by evaporation (Savant Speed Vac) and reconstituted in 0.25 ml of radioimmunoassay buffer. Immunoreactive endothelin-1 was measured with a commercial radioimmunoassay kit (Amersham International). The intraassay coefficient of variation was 4.6 percent, and the interassay coefficient of variation was 16.2 percent.

Although there was substantial overlap between the groups, the mean (±SE) level of plasma endothelin was significantly higher in patients with Raynaud's phenomenon than in controls (2.19±0.41 vs. 0.77±0.18 pg per milliliter; $P<0.02$ by Student's t-test). No significant differences in the levels were found between patients with primary and those with secondary Raynaud's phenomenon (2.55±0.65 vs. 1.83±0.53 pg per milliliter) (Fig. 1). For both patients and controls, plasma endothelin levels were independent of age. These preliminary data suggest that plasma endothelin levels are significantly increased in some patients with Raynaud's phenomenon. Further study is necessary to elucidate the mechanism

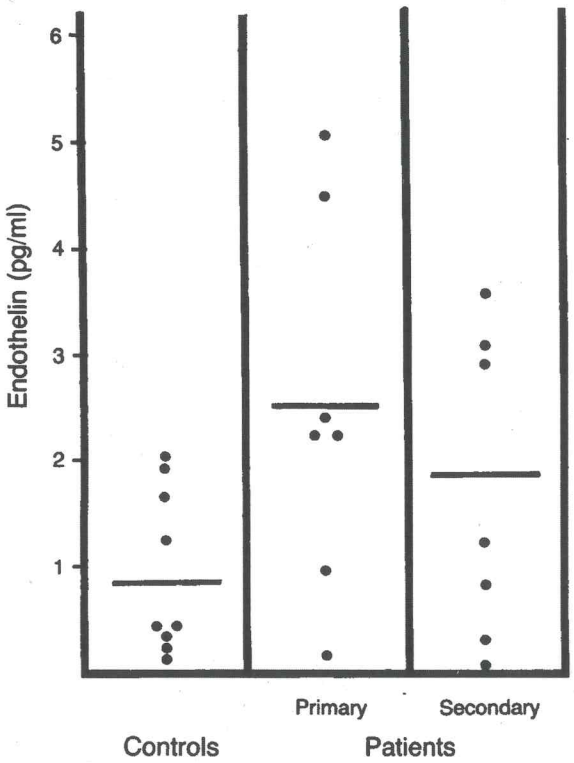

Figure 1. Plasma Endothelin Levels in Controls and in Patients with Primary or Secondary Raynaud's Phenomenon. Bars represent means.