"Mineral Transporter" Therapy for Multiple Sclerosis Complicated by Bacterial Endocarditis

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Medical nostrums and miracle cures have been popular throughout history. Many such treatments are benign. Danger does exist, however, when recognized beneficial therapy is rejected or delayed in favor of these "cures." Dangers resulting directly from unsubstantiated treatments may be difficult to foresee, as our case illustrates.

A 65-year-old man with a 30-year history of multiple sclerosis (A1 score in the Clinically Definite Multiple Sclerosis category [2]) was seen because of chronic fever, night sweats, anorexia, and exacerbation of neurological symptoms. Six weeks earlier he had traveled to Hannover, Germany, and undergone "mineral transporter" therapy.* This consisted of daily intravenous injections of calcium-2-aminoethanol phosphate supplemented by orally administered calcium and intramuscular vitamin B_{12}. Since returning, his treatment was continued using drugs imported from Germany. Syringes and needles were procured at a local hospital by his daughter, a registered nurse.

The patient had a childhood history of rheumatic heart disease and 5 years earlier had undergone Carpentier-Edwards mitral valve replacement. His other medications included prednisone, warfarin, Pro-Banthine, and Dyazide.

Examination revealed an exhausted febrile man without splinter hemorrhages or Roth's spots. There was a murmur caused by aortic insufficiency. He exhibited dysarthric speech, spastic triparesis, and bilateral Babinski signs. His white blood cell count was elevated, and multiple blood cultures grew *Streptococcus bovis*. A diagnosis of *S. bovis* endocarditis was made and antibiotic therapy was initiated. Echocardiography failed to demonstrate valvular vegetations. Endoscopy of the lower gastrointestinal tract yielded normal findings. The patient returned to his baseline neurological status after two weeks of therapy.

At our institution, *S. bovis* accounts for 20% of the cases of streptococcal endocarditis, which in turn accounts for 50% of the cases of infectious endocarditis. *S. bovis* endocarditis has increased in incidence while that caused by *S. viridans* has decreased and currently accounts for 25% of all cases of streptococcal endocarditis [1]. Approximately 50% of all patients have an antecedent history of genitourinary tract instrumentation or trauma, or are found to have a gastrointestinal carcinoma. Bacterial endocarditis is more common in the presence of prosthetic heart valves and in intravenous drug addicts [3].

A causal relationship between endocarditis and intravenous therapy in our patient could not be established. Cultures of the patient's skin and bottled drugs failed to grow *S. bovis*. Although he did have a history of frequent bladder catheterization, urine cultures also did not yield the organism.

Homeopathic or extra-medical treatments are often presumed to be benign. As a consequence, the inability to treat many degenerative neurological diseases may lead practitioners to turning a blind eye when patients seek unsubstantiated treatments. This may be because we hope the treatment will produce some benefit, and even that the patient will serve as an informal experimental subject. It is obvious that the risk of alternative therapy must be determined from case to case. Home intravenous therapy may be safe in certain settings. In the presence of a prosthetic heart valve, however, it is contraindicated.

*A description of this regimen may be obtained from the A. Keith Brewer Scientific Library, Admiral Ruge Archives, Richland Center, WI 53581.

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Tetrabenazine and Dystonia in Primates

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Burke and colleagues [1] have described acute dystonic reactions induced by tetrabenazine (TBZ), a monoamine-depleting agent, in neurological patients. These observations may have been anticipated by our preclinical findings using a primate model [2]. In squirrel monkeys with a history of prior neuroleptic treatment, an acute dyskinetic syndrome can be elicited by dopamine antagonists such as haloperidol or metoclopramide [2, 6]. This syndrome resembles acute dystonic reactions in that (1) torticollis and dystonic postures are evident; (2) anticholinergics and diazepam block the syndrome; and (3) the syndrome dissipates as the drug wears off and never occurs when the animals are in a drug-free state. Acute administration of TBZ induces the syndrome in susceptible monkeys [2]; repeated administration of TBZ to previously drug-naive monkeys renders them susceptible to the syndrome [3]. Although Burke and colleagues suggested that TBZ induces acute dystonic reactions by dopamine blockade rather than by catecholamine depletion, this does not appear to be the case in the animal model. D-Amphetamine reverses TBZ-induced acute dystonia and dyskinesia, presumably by restoring synaptic catecholamine release, but does not reverse haloperidol, a directly acting dopamine antagonist [4].

Another catecholamine depletor, α-methyl-para-tyrosine, can induce the acute dyskinetic syndrome in squirrel monkeys [4], which is compatible with the worsening of acute dystonic reactions by this drug in one patient described by Burke's group. The syndrome is also induced by the cholinergic agonist arecoline [4]. These and other findings led to the proposal that this animal model is characterized by an acute imbalance in dopamine and acetylcholine transmission [4]. The conclusions drawn by Burke and associates for acute dystonic reactions are in complete agreement. The animal model offers the potential for elucidating mechanisms involved in neuroleptic-induced extrapyramidal disorders.

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Reply

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We are grateful to Dr Liebman for bringing to our attention his finding that tetrabenazine (TBZ) induces acute dyskinesia in squirrel monkeys. The description of some of the involuntary movements in these animals, including writhing movements and persistent extension of the limbs, does suggest a resemblance to human acute dystonia. These dyskinesias also resemble acute dystonia in their time course and their clinical pharmacology. Our report that TBZ induces acute dystonia in humans provides further evidence of similar clinical pharmacology. One major difference, however, between human dystonic reactions and squirrel monkey dyskinesias is that the latter require chronic pretreatment with neuroleptics. In this respect they bear a closer resemblance to human tardive dyskinesia. In addition, some of the dyskinesias include licking, biting, and tongue protrusions, which are features of tardive dyskinesia. Nevertheless, we agree with Dr Liebman that most of the evidence, especially the clinical pharmacology, suggests a relationship to acute dystonia.

Dr Liebman makes the very good point, based on experiments in monkeys, that the ability of TBZ to induce acute dystonia may be due to its catecholamine-depleting properties rather than its dopamine receptor–blocking properties. We postulated that the receptor-blocking properties were responsible, based on the universal ability of dopamine receptor–blocking drugs to induce acute dystonia, and the inability of reserpine, another catecholamine depletor, to do so. However, we recognize that other pharmacological differences between TBZ and reserpine, besides the receptor-blocking properties of TBZ, may explain the ability of TBZ, and not reserpine, to induce acute dystonia. For example, TBZ depletes catecholamines more rapidly than does reserpine [5]. Perhaps it is the rapidity of inhibition of central dopaminergic transmission, rather than blockade, that is critical for the induction of acute dystonia.

Dr Liebman's observation that the cholinergic muscarinic agonist arecoline is able to induce acute dyskinesias is fascinating in view of the hypothesis that human acute dystonic reactions may be due to a sudden overactivity of central cholinergic systems.

We agree that these animals offer potential for an improved understanding of neuroleptic-induced movement disorders in humans.

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Dysglobulinemic Neuropathy: Absence of Immunoglobulin within Myelin Sheaths

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Peripheral neuropathy occurs in association with some plasma cell dyscrasias, including monoclonal gammopathy of undetermined significance [2]. Using immunofluorescence techniques, some investigators have found immunoglobulin in the myelin sheaths of peripheral nerves from patients with monoclonal gammopathy [1, 4, 6, 7]. Serum immunoglobulins from some patients with dysglobulinemic neuropathy have also been found to bind to myelin sheaths in normal nerve tissue [4, 6] and to a myelin-associated glycoprotein separated from other myelin proteins [3, 4, 6]. Thus, the uniform separation of the intraperiod lines of myelin sheath that sometimes is seen in peripheral nerves of dysglobulinemic patients during electron microscopic study [4–6] has been attributed on a theoretical basis to immunoglobulin deposition.

We describe observations on nerves from two patients who had a peripheral neuropathy associated with a serum IgM kappa monoclonal protein of undetermined importance. The clinical features of the patients have been reported as Cases 4 and 5 in [5]. The number of myelinated fibers was decreased in sections of peripheral nerves from both patients; electron microscopy showed the myelin lamellae to be uniformly separated (Figure, A). The initial goal of the study was to demonstrate convincingly the deposition of Ig within