Editor-in-Chief's Note

Comments on Chronic Fatigue Syndrome

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This month's Update, developed by Dr. Theoharis C. Theoharides, our Topic Editor for Allergy, Asthma, and Immunology, is the first of a two-part series focusing on chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis or systemic exertion intolerance disease.[1–8] A second collection of related papers will appear in our May issue.

One of the earliest patients I treated after finishing my training was a 30-year-old man with extreme exhaustion, whom I shall call Dominic Teague (DT). DT was referred by his family physician (FP), who had concluded that DT was depressed. DT had consulted his FP because of excessive tiredness that had lasted for 6 months. The son of a nurse, DT was feeling hopeless and worried that he was anemic. His FP's workup revealed no obvious reasons for his tiredness. DT was a successful professional who had enjoyed running, both for exercise and relaxation. Now, whenever he ran even a short distance, he was exhausted. I learned that he was currently bothered by headaches which were not migraine-like; rather, to me they sounded like tension headaches. He also described interrupted sleep. I also learned that, at age 20, he was diagnosed with infectious mononucleosis (aka "mono"). At that time, he had been told that he tested positive for Epstein–Barr virus (EBV) antibodies; his blood count also revealed elevated lymphocytes. His family history was negative for any disorder of mood, and no one had ever described being tired to the degree he was. He had not told his FP about his bout of mono, saying he had not been asked about it and that it had not occurred to him that it could be relevant after so many years.

I considered that DT might be one of those rare people who have chronic or recurrent mono.[9] When chronic mono is present, certain EBV-related antibodies are usually found. These include viral capsid antigens immunoglobulins M and G and EBV nuclear antigen 1 immunoglobulin G. Dr. Henry Balfour, director of the Epstein–Barr Diseases Research Program at the University of Minnesota, recommends treatment with specific antivirals, depending on the antibodies present.[10] However, DT's monospot test[11] result was negative and his blood count was normal.

I asked DT about his consumption of alcohol, particularly because of his fragmented sleep. He was a devotee of single-malt scotch, which he often drank at night to help him fall asleep. He had tried stopping it, but he said it made no difference in his sleep pattern or energy level. At DT's second appointment with me, I decided that DT was demoralized rather than depressed. At times of day when he was not tired, he was able to enjoy relationships, food, and entertainment. He just seemed defeated by his tiredness and his lack of success at finding relief. My conclusion was that Dominic Teague had chronic fatigue syndrome.

After DT's second appointment, I conducted a literature search, which uncovered no adequately sized randomized, controlled trials of products (drugs or supplements) that demonstrated efficacy (consistent or persistent symptom relief) in patients with CFS. In 2016, Collatz et al[12] reported on a systematic review of pharmacotherapies for CFS, concluding that "no universal pharmaceutical treatment can be recommended." Twenty-six studies from a total of 1039 published reports met their criteria for additional scrutiny. Of the 26, one involved the psychostimulant dextroamphetamine.[13] Another involved the CNS stimulant modafinil,[14] and two involved the monoamine oxidase inhibitors phenelzine and meclobemide.[15,16] I recently found three additional reports covering methylphenidate, lis-dextroamphetamine, and modafinil.[17–19] The first two studies were inconclusive, small-sample trials, and the modafinil report was about a positive response to modafinil in a single case. I also examined the 104 CFS

studies currently listed on ClinicalTrials.gov [20]; only three describe results. Of these three, one is mentioned above,[18] and the other two are not yet published.

Returning to DT, I decided to give him a 3-week, off-label trial of tranylcypromine (TCP).[21] TCP was first synthesized as an amphetamine analogue. It is formed via cyclization of the side chain of amphetamine. TCP is a nonhydrazine, irreversible inhibitor of both monoamine oxidases A and B. When I prescribed it for DT, I made the erroneous assumption that one of its metabolites was amphetamine; I had heard this at a lecture and did not realize that the pharmacology of TCP had not yet been fully characterized. Subsequently, it became clear that TCP has no amphetamine or amphetamine-like metabolites.[22,23] DT's trial began with TCP at 10 mg bid for week 1. For weeks 2 and 3, the dose was increased to 20 mg in the morning and 10 mg in the late afternoon. To assess any clinical improvement, he agreed to use a self-rated, 10-point global fatigue/discomfort scale on which 10 equaled extreme fatigue. He rated himself at 9 when we initiated treatment with TCP. He did not feel any change for the first several days. By the end of the first week, he rated himself at 7. After 3 weeks, he rated himself at 4. I followed him up on the 30-mg dosage regimen for the next 6 months, during which his scores fluctuated between 3 and 4. He never felt a complete return to his healthy, energetic self. Because he commuted quite a distance to see me, he asked his FP to take over prescribing TCP. I should mention that he disliked being on a tyramine-free diet; pizza was his favorite food. In preparation for this Note, I tried unsuccessfully to learn what became of DT. His FP died a few years ago; no records were accessible to me. Readers may wonder why I did not try higher dosing. My recollection is that I was wary because I had limited experience with TCP at that point in my career, and I wanted to avoid any side effects; he had none at the 30-mg dosage.

In my view, ME/CFS continues to be one of those mysterious immune system—related syndromes that likely have multifactorial underpinnings. I hope we will return to this topic in a future Update and find that additional progress has been made.

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This month's Allergy, Asthma, and Immunology Update is a special feature which is available as FREE ACCESS content on the journal's website. One of the previous Allergy, Asthma, and Immunology Updates, entitled "Mold and Immunity" was published in Volume 40, Number 6 of Clinical Therapeutics. To view the previous Update, see the articles below:

Theoharides TC. Mold and Immunity.

Conti P, Tettamanti L, Mastrangelo F, et al. Impact of Fungi on Immune Responses.

Rea WJ. A Large Case-series of Successful Treatment of Patients Exposed to Mold and Mycotoxin.

Petrikkos G, Tsioutis C. Recent Advances in the Pathogenesis of Mucormycoses.

Ratnaseelan AM, Tsilioni I, Theoharides TC. Effects of Mycotoxins on Neuropsychiatric Symptoms and Immune Processes.

Vrioni G, Theodoridou K, Tsiamis C, et al. Use of Galactomannan Antigen and Aspergillus DNA Real-time Polymerase Chain Reaction as Routine Methods for Invasive Aspergillosis in Immunosuppressed Children in Greece.