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About Our Cover

This monarch butterfly (*Danaus plexippus*) chrysalis (pupa) was attached to a common milkweed (*Asclepias syriaca*) plant found in Westminster West, Vermont. The monarch chrysalis starts as a pale green color, speckled with glistening dots of gold, and becomes transparent just before the adult butterfly emerges. When this specimen emerged it was easily identified as a male by the black oval scent patch located on each hindwing.

In mid- to late May, monarchs arrive in New England from the wintering grounds in the Sierra Madre of central Mexico. Once they reach their summer habitat, they lay eggs on the underside of milkweed leaves. One female can lay up to five hundred eggs in her lifetime. The caterpillar will spend up to two weeks eating and growing before transforming into a chrysalis.

The adult butterflies born in New England in late July and August do not reproduce immediately because of decreasing light and dropping temperatures. Instead they spend their time feeding on nectar in preparation for the arduous migration south. During the fall months this generation of adults migrates to the overwintering sites in Mexico. In early spring, the overwintered generation will begin the journey north and lay eggs to begin a new generation. It can take as many as three or four generations before the monarchs reach New England again, making the ones that arrive the great and great-great grandchildren of the overwintering monarchs.

This photo was taken by Abigail P. Littlefield, Professor of Natural Science (retired) at Landmark College (Putney, Vermont), using an Olympus E-M10ii with a macro lens, F8, ISO 800.

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Chronic Fatigue Syndrome & Other Difficulties: Introducing a Modern Scientific Controversy to a Biology Classroom

JUN LIANG, IGOR V. ZAITSEV



ABSTRACT

One of the most perplexing dilemmas in modern science is chronic fatigue syndrome (CFS). Even though the illness was recognized at the beginning of the 20th century, the pathogenicity and etiology of the disease remain unknown. We describe an open-inquiry case study on CFS that we have used in our biology classrooms to increase students' critical-thinking skills and understanding of scientific method. Three general categories of potential pathogens – virus, vaccine, and microbiome – are discussed during multiple classroom sessions. We found that our students were more proactive than expected. They researched credible references from the most recent publications and formulated arguments on the medical issue. They applied knowledge of human body systems to explain the complexity of the disease. Students were capable of distinguishing “correlation” and “cause” relations between the disease and pathogens. We observed a high level of student participation and involvement, which not only increased their knowledge of scientific approaches but also strengthened their interaction and communication skills. The case study is suitable for biology courses in both high school and college.

Key Words: Chronic fatigue syndrome; pathogen; symptom; diagnosis; human body system; critical thinking; scientific method.

○ Introduction

The study of chronic fatigue syndrome (CFS) is a matter of significant controversy in modern science. Even though the illness was recognized at the beginning of the 20th century and millions of dollars were poured into studies of it, we still don't know, at this late date, much about its etiology or pathogenicity. As debates and discussions continue, one of the researchers has claimed, “We don't have agreement on almost anything” (Kaiser, 2010). It is a disease doctors refuse to see; they aren't persuaded by the scientific evidence (Rehmeier, 2015).

*“It is a disease
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Taking into consideration the vast amount of theoretical topics and applied approaches covered in those debates, as college biology professors, we recognize the value and relevance of this enigmatic disease as a subject in our lectures (Zaitsev, 2009b; Zaitsev et al., 2013). It not only helps us review some of the topics of biochemistry, but also enhances coverage of the unit on the human body system. Implementation of some research conjectures demonstrates the tentative nature of science and induces students to think analytically and critically (Zaitsev, 2009a, 2010). This article will provide information on the peculiarity of the enigmatic disease and the controversy surrounding it so that it can be introduced to biology classes in both high schools and colleges.

○ Background on CFS: Being Sick & Tired

When most people become tired, rest or sleep will usually rejuvenate them. In people with CFS, fatigue is resistant and excessive and does not improve with either rest or sleep. It may be aggravated by physical or mental activity (CDC, 2012), causing extreme exhaustion. Other common signs and symptoms include unexplained muscle and joint pain, atypical headache, enlarged lymph nodes, mild fever, a wide range of gastrointestinal difficulties, and inability to sleep or to sleep deeply. These non-specific signs and symptoms are similar to those of many other illnesses such as anemia, hypothyroidism, Lyme disease, depression, and others. Many psychiatrists speculate that the condition is the product of profoundly psychological or behavioral causes (Prins et al., 2006; Deary & Chalder, 2010). A survey of 811 physicians revealed that 44% did not feel confident making the diagnosis of CFS (Bowen et al., 2005).

○ The Controversy

Lately, more evidence has accumulated demonstrating that CFS is a serious physical disability that is not caused by psychosis but is a result of complex pathophysiological processes in the human body. It is deemed more appropriate to use the term *myalgic encephalomyelitis* (ME) since it indicates an underlying pathophysiology (Carruthers et al., 2011), which might cause neurological changes (Tirelli et al., 1998; Chen et al., 2008), cardiovascular abnormalities (Peckerman et al., 2003; Hollingsworth et al., 2010), endocrine dysfunction (Hyde, 2007), and immunopathology (Lorusso et al., 2009; Broderick et al., 2010), among many other pathologies.

Some researchers differentiate between CFS and ME, specifying that the latter is an acute illness that often becomes chronic (Jason et al., 2012), but in mainstream usage these terms are interchangeable. It is characteristic of CFS/ME that signs and symptoms come and go (fluctuate). The disease affects both sexes and all racial, age, and socioeconomic groups (Jason et al., 1999). It may exhibit a sudden onset or come on gradually. Some patients improve spontaneously, but many others experience a prolonged course of the disease with periods of remission and exacerbation (U.S. Food and Drug Administration, 2013). Diagnostics are based purely on clinical symptoms using nothing but self-report questionnaires (Morris & Maes, 2013), and there are no explicit testing methods to pinpoint this illness specifically. There are also no common agreements on the diagnosis; different scientists and health organizations use different core symptoms to diagnose CFS/ME (reviewed by Jason et al., 2012). Some take post-exertional malaise as a hallmark for diagnosis (“London,” Hyde, and Goudsmit criteria) while others rely on fatigue that does not get resolved with bed rest (Holmes et al., U.S. Centers for Disease Control and Prevention [CDC], and Canadian criteria) (Table 1). Understandably, the latter three, especially the recent CDC empiric criteria (Reeves et al., 2005), have expanded the pool of CFS/ME patients. The Fukuda criteria, which require four out of eight symptoms (Table 1), constitute the most widely used definition in CFS/ME research, but many limitations and challenges remain with regard to these polythetic criteria. The time period required for diagnosis varies among the different criteria. The Goudsmit criteria require the major symptom to be present for three months, whereas most of the others require six months. However, the Hyde criteria do not suggest a specific time period. More recently, Carruthers et al. (2011) proposed new hallmarks for the definition of CFS/ME – referred to as International Consensus Criteria – that require the patient to have post-exertional neuroimmune exhaustion plus one symptom from each of three categories (Table 2). Shortly after the latter criteria were published, the Morris-Maes criteria appeared in the journal *Neuroendocrinology Letters* (Morris & Maes, 2013). Morris and Maes criticized the International Consensus Criteria and proposed the use of neuroimmune biomarkers in CFS/ME diagnosis. The historical development of the different criteria purporting to select patients with CFS/ME is described in detail by Jason et al. (2012), Morris and Maes (2013), and Sunnquist et al. (2017).

The numerous disagreements in the research community triggered a bureaucratic response from the U.S. government. The U.S. Department of Health and Human Services and the nonprofit Institute of Medicine requested a study to produce new criteria and definitions for CFS/ME (U.S. Department of Health and Human Services, 2013).

Certainly, until there is a final understanding of the nature of CFS/ME, there will be tension not only between doctors and patients but between the CFS/ME community and government officials. Reports show that 1–4 million people in the United States are affected by CFS/ME (U.S. Food and Drug Administration, 2013), which has substantial economic costs. By the most modest estimation, costs to the U.S. economy due to CFS/ME are in the range of \$17–24 billion (Jason et al., 2008).

○ Everybody’s Viruses – Innocents or Not?

In the 1860s George Beard, a New York neurologist, identified a syndrome that he called neurasthenia. His description of the syndrome is quite similar to what we now call CFS/ME. He assumed that this elusive disease was a neurosis with a fatigue component and suspected that it had a biological basis (Rosenberg, 2007). There were numerous CFS/ME outbreaks in groups of people in various parts of the world throughout the 20th century (Acheson, 1959; Daugherty et al., 1991; Patarca-Montero, 2004). This led research experts to hypothesize that CFS/ME might be of an infectious nature. Some of the suspects were and still are herpesviruses, which are truly “everybody’s viruses.” At certain periods of life, we acquire these ubiquitous pathogens and then harbor them the rest of our life. Most of us are unaware of the infection because no noticeable signs or symptoms appear. They hide in our cells and become latent. However, when the human immune system becomes assaulted by temperature, radiation, additional infections, or other physical or mental stressors, some of them reactivate and cause a variety of conditions, from very mild to life threatening.

One such pathogen is the Epstein-Barr virus (EBV), also called human herpesvirus 4 (HHV-4). It is estimated that 95% of Americans have been infected with the virus by adulthood (Rickinson & Kieff, 2001). EBV is an etiologic agent of infectious mononucleosis (Epstein & Achong, 1973) and several types of tumors and is transmitted through saliva. Although most people who contract EBV do not experience an active illness, some infected individuals immediately experience a state of chronic fatigue. Reports suggest that partially reactivated EBV could function as a biomarker for certain illnesses, including CFS/ME (Lerner et al., 2010). In 1986, human herpesvirus 6 (HHV-6) was discovered. As it turned out, over 95% of the population is infected with HHV-6 by age three (Braun et al., 1997). Like EBV, it is transmitted through saliva. This virus is an etiologic agent of the childhood disease called roseola and has been associated with a variety of potentially life-threatening complications in immunocompromised people, while in healthy individuals the virus remains inactive. Interestingly, unlike other herpesviruses, the DNA of HHV-6 integrates itself into the telomere structures at the end of chromosomes, where it remains latent and can be transmitted vertically from parent to child. This condition is known as chromosomally integrated HHV-6 (CIHHV-6; Pantry et al., 2013). Extensive research on HHV-6 led to the discovery of its closest sibling, human herpesvirus 7 (HHV-7), in 1990. The latter was first discovered from T-cells of a healthy donor and a patient with CFS/ME. As with HHV-6, 95% of the population is infected with HHV-7. Over 75% are infected before six years of age. However, some studies indicate that HHV-7 could be associated with CFS/ME

Table 1. Criteria and core symptoms used in CFS/ME diagnosis (reviewed by Jason et al., 2012).

Criteria	Symptoms											≥3 Months	≥6 Months
	Fatigue Not Resolved with Bed Rest	Post-exertional Malaise	Memory and Concentration Impairment Plus Disturbed Sleep	Vascular Damage in the Central Nervous System	Circulatory Impairment	Cardiac Irregularity	Endocrine Dysfunction	Presence of Viral Illness	Fluctuation of Symptoms				
"London" ME criteria		+	+		+			+	+			+	
Hyde ME criteria		+			+	+	+						
Goudsmit ME criteria		+									+		
Holmes et al. CFS criteria	+											+	
CDC CFS criteria	+	+										+	
Canadian ME/ CFS criteria	+		+									+	
Fukuda CFS criteria	Four symptoms out of the following eight: impaired memory or concentration; sore throat; tender cervical or axillary lymph nodes; muscle pain; multi-joint pain; new headaches; unrefreshing sleep; post-exertion malaise.												+

Table 2. The International Consensus Criteria (Carruthers et al., 2011) require one symptom from each of the three categories shown here, in addition to post-exertional neuroimmune exhaustion, for CFS/ME diagnosis.

Neurological Impairments	Immune, Gastrointestinal & Genitourinary Impairments	Energy Production/Transportation Impairments
Neurocognitive impairments (difficulty processing information and short-term memory loss)	Often flu-like symptoms	Cardiovascular abnormalities
Pain (abdominal pain, headaches, myalgias, arthralgias)	Often viral infections with prolonged recovery periods	Respiratory symptoms (fatigue of chest wall muscles, air hunger, etc.)
Sleep disturbance (disturbed sleep patterns or unrefreshing sleep)	Gastrointestinal tract disturbances (irritable bowel syndrome, bloating, nausea)	Loss of thermostatic stability (cold extremities, sweating episodes, etc.)
Neurosensory, perceptual, and motor disturbances	Genitourinary problems (nocturia, urinary urgency)	Intolerance to extremes of temperature
	Sensitivities to foods, medications, odors, or chemicals	

(Chapenko et al., 2012). It could be involved in the exacerbation of its close relative cytomegalovirus (CMV), or human herpesvirus-5 (HHV-5), known since the 1950s. The transmission of the CMV occurs via saliva, urine, semen, and milk. The vast majority of people throughout the world are infected with HHV-5. The virus does not cause any diseases in immunologically competent individuals. In its latent form, CMV “lurks behind appearances and acts like fifth columnists who can activate into a lytic infection and subvert the host” (Ho, 2008). It is an etiologic agent of cytomegalovirus diseases that occur in 21–44% of AIDS patients (Gallant et al., 1992) if antiretroviral therapy is not administered. It also has been suggested that parvovirus B19, an etiologic agent of childhood rash diseases (Vafaie & Schwartz, 2004), may be involved in the pathogenesis of CFS/ME (Frémont et al., 2009). Outbreaks of the disease usually arise in nurseries and schools. Although it is most common in children six to ten years old, any age may be affected.

It is common for people with CFS/ME to have several infections at the same time. According to the latest observations, the trinity of HHV-6, HHV-7, and parvovirus B19 might be the cause of CFS/ME (Chapenko et al., 2012). The reactivation of these viruses is accompanied by increased levels of two biochemical compounds that play a central role in inflammation processes: (1) tumor necrosis factor alpha (TNF- α) and (2) interleukin 6 (IL-6) (Komaroff & Buchwald, 1998; Chapenko et al., 2012). It has long been known that TNF- α and IL-6 induce a systemic inflammatory response in which one of the major symptoms is severe fatigue (Lakhan & Kirchgessner, 2010). Thus, a role for TNF- α and IL-6 as an immunomodulating trigger factor in CFS/ME should not be excluded, and further research must be done in this area. It has become clear that CFS/ME is not caused by a single agent; rather, the syndrome results from the interplay of several factors, including the peculiarity of the host's immune system as determined by genetic makeup.

○ Everybody's Vaccines

Because many vaccinations typically result in a flu-like illness in which fatigue is routinely present, there is a long list of vaccines

that have been falsely accused of causing CFS/ME, including vaccines with which most of the population have been vaccinated. Examples include MMR, Pneumovax, influenza, hepatitis B, tetanus, typhoid, and poliovirus vaccines (Devanur & Kerr, 2006). It has been speculated, on an anecdotal basis, that vaccines may cause CFS/ME through the initiation of an autoimmune response (Lloyd et al., 1988; Weir, 1992). To date, there is no evidence for such a hypothesis. However, given that these speculations sporadically appear in social media and on the websites of complementary and alternative medical providers, as well as on anti-vaccination websites, it is essential to address the issue. Students should be referred to peer-reviewed journals instead of social media and other websites.

○ Microbiome

The human body hosts a large variety of microorganisms, and human health is tightly related to the types of microbes living on and within the body (Martinez-Guryn et al., 2018; Mikó et al., 2018). Because of the microbiome's importance, microbiome-based laboratory exercises have recently been introduced at the college level (Zaitsev, 2015). It has been reported that the microbiome may also play a role in CFS/ME (Maxmen, 2018).

○ Classroom Activities & Assessment

The case study described here is suitable for biology courses in high schools and colleges. It is a particularly attractive choice for human anatomy and physiology courses, as well as for microbiology courses geared toward health-care majors. The complexity of CFS/ME requires a variety of criteria and methods for diagnosis. In addition to the case study, we provided our students with information on the possible role of herpesviruses in CFS/ME and discussed a number of such viruses. As noted above, these viruses are widespread in the human population, which should lead students to question whether they might cause CFS/ME. The information presented should also

elicit students' interest in learning more about the possible roles of vaccines and the microbiome in CFS/ME (we deliberately cut discussions of the latter short so that students were free to research and explore available information from all sources). We have usually followed the format of the sessions described in Zaitsev (2009b). The case study was given at the end of the semester, so that students were already familiar with the basic structure and functions of human body systems. The learning outcomes of the case study are as follows:

- (1) Students will be familiar with symptoms of a disease and the complexity of diagnosis.
- (2) Students will be acquainted with the scientific method, research strategy, and peer-reviewed journals.
- (3) Students will formulate arguments concerning a controversial scientific issue and make a presentation.
- (4) Students will integrate their knowledge to make interdisciplinary connections.

○ First Session: The Mysterious Syndrome

In our classes, students usually were given the case study (see Box 1) two weeks before the scheduled oral presentation. Each group consisted of four students, and there were six groups in each class. Each group chose one of the following six topics to present in front of the class:

- (1) General Review of CFS/ME
- (2) Contribution of Virus to CFS/ME
- (3) Contribution of Vaccine to CFS/ME
- (4) Contribution of Microbiome to CFS/ME
- (5) Treatment of CFS/ME
- (6) Innovative approaches to diagnosing and treating CFS/ME

Each topic represents an important aspect of the disease. Students were instructed to read the case study and focus on their own topic. Questions in the case study provide guidelines for preparation of the presentations. To introduce CFS/ME, the case study starts with a character in a well-known TV show; the controversy over whether it is a real disease and how to diagnose it follows.

Box 1: Case Study

The Golden Girls is a popular TV sitcom (1985–1992) still shown in reruns. The plot involves four compatible, unattached, retired women who share a house in Florida. In season 5, episode 2 ("Sick and Tired"), Dorothy Hollingsworth, one of the women, has been complaining of extreme exhaustion, which her physician dismisses as either hypochondria or depression. Other doctors with whom she consults concur until Dr. Chan tells her that she is suffering from chronic fatigue syndrome (CFS). Relieved that her condition has finally been identified, she goes to a restaurant with her mother and housemates to celebrate. At the next table she notices the physician who had dismissed her complaints as imaginary. Unable to resist

confronting him, Dorothy gives vent to the frustration of having suffered, as many CFS patients have, not understanding why their physicians dismiss them. Enraged, Dorothy says that "I do not know where you, doctors, lose your humanity, but you lose it." She concludes her tirade: "You better start listening to your patients. They need to be heard. They need caring. They need compassion. They need attending too. You know, someday, Dr. Bird, you will be on the other side of the table. And as angry as I am, and as angry as I always will be, I still wish you a better doctor than you were to me."

This episode of *The Golden Girls* demonstrated a need for social awareness of a debilitating and complex disorder that had been trivialized due to the lack of scientific evidence supporting its diagnosis. CFS was dismissed for decades as the "yuppie flu" and widely regarded as a psychosomatic disorder (Palca, 1991). Chronic fatigue sufferers were often treated with sarcasm and skepticism by family, friends, and coworkers who accused them of *malinger*ing. This led CFS patients to feel demoralized, frustrated, and angry.

Questions:

- (1) On what basis would you think Dr. Chan was able to diagnose Dorothy?
- (2) What criteria are used by doctors to diagnose patients with CFS today?
- (3) Could something like the story portrayed in this *Golden Girls* episode, written more than 20 years ago, happen today?
- (4) Write a list of questions that patients might be asking their physicians about this disease today.

In each group, students divided among themselves the workload responsibilities for the presentation. Since CFS/ME is still controversial in medical research, students were instructed to be impartial during collection of information. Students were required to use figures and graphs from other publications in their presentation. They were also encouraged to prepare questions for their classmates who would be presenting on other topics, which ensured that each group's presentation had engagement from their peers. We asked each group the following questions:

- (1) In 2009, a research team led by principal investigator Judy Mikovits reported that xenotropic murine leukemia virus (XMRV) causes CFS/ME (Lombardi et al., 2009). Since that report, there have been many debates over whether a single virus could lead to CFS/ME. What is your opinion and why?
- (2) A principal investigator in a CFS/ME study purposely removed lab notes from the research lab she was in charge of. Was this action lawful? Explain.
- (3) Do you think that CFS/ME affects a person's mental health? Explain.
- (4) In 2017, the National Institutes of Health (NIH) announced it would provide over \$7 million to study CFS/ME. This demonstrates an ongoing need for this type of research. What do you think should be investigated first?

○ Second Session: Simmering Controversy

Students were more proactive than we anticipated. They found many new references that are not listed in the case study, including some recent research studies. They also found that there was a recent attempt to rename CFS/ME as “systemic exertion intolerance disease.” Some students appeared to be skeptical about this endeavor, since researchers could not agree upon the various definitions of the disease and there were no definitive medical tests that could be used for diagnosis.

Students applied their course knowledge to describe symptoms of CFS/ME affecting various body systems, such as the immune system and nervous system. The case study reinforced concepts learned in the lecture. For example, the group focusing on vaccination applied the mechanism of immune response. During their presentation, students explained (1) what a vaccination is, (2) how it impacts the immune system in humans, (3) which cells are triggered by immune responses, and (4) how antibodies are generated. They even found a court case in the United States in which a young patient won \$250,000 compensation for having developed CFS/ME after being given a hepatitis B vaccination. They also brought up relevant data from the the Canadian Laboratory Center for Disease Control that show no evidence to support that finding of causation.

Students who focused on CFS/ME treatment elaborated on neurotransmitters, on antidepressant medications given to CFS/ME patients, and on the role of antioxidants in improving patients' condition. Students were also aware of the challenges of treatment. For instance, antidepressants could give a patient suicidal thoughts. Some students knew about side effects of these medications from their own life experience and brought valuable arguments to the classroom. There was an exciting discussion on this topic.

Most students realized that there might be a correlation between CFS/ME and the proposed “pathogenic agents.” In the classroom, students inquired why some people who have been infected with the same viruses or who have received the same types of vaccine do not have CFS while others do. They were confident in articulating their opinions. For example, they argued that those agents themselves might not cause the disease; the patient might have other underlying, contributing medical conditions, such as HIV, or a combination of various agents might trigger the disease. They cited relevant research to demonstrate their findings. Students distinguished between “correlation” and “cause,” indicating that they comprehended fundamental aspects of pathology in medicine. However, students usually were unsure how to further their discussion.

The group assigned the last topic – on future directions of CFS/ME research – did not fully understand their challenge. They mostly gave an overview of CFS/ME research rather than offering possible perspectives. It was a difficult topic to present, since the students were not experts on CFS/ME; however, they did find some useful information in research on CFS/ME. For example, they found that there is 200× more funding for HIV than for CFS/ME. They explained that this is due to the lack of definite explanations of the nature of CFS/ME. Students advocated for more patient sample analysis and the search for biomarkers.

Students showed that they were capable of conducting independent research using credible resources such as peer-reviewed research articles, patient pictures, court cases, and others. All groups included figures and graphs from such reference materials in their presentations. In presenting these scientific analyses, students demonstrated their critical-thinking skills.

When given the case study, students started with an uncertainty about CFS/ME. To them, a person with this syndrome seemed more or less like a person who does not want to work, who just feels tired all the time. However, after their own research on CFS/ME, many of the students had revised their opinions on the disease. In the end, students were asked in a survey whether they believed that CFS/ME is an actual physical disease or rather a psychological problem. Half of the class believed that it is a real disease and the others did not.

Interestingly, we also found that students justified their opinions using anthropology and sociology studies from other disciplines. For example, to explain why most of the patients diagnosed were white women in the United States, some students suggested that women are more outspoken than most men. Meanwhile, the white population has more access to good health care than minority populations. However, that does not mean that CFS/ME does not exist in minority populations. Approximately 3.9 million minority individuals were potential CFS/ME patients, based on the students' findings.

The painting reproduced here as Figure 1 captures the frustration and despair of a CFS/ME patient, putting a human face on the problem. Our college has an Arts Across the Curriculum program



Figure 1. *Defeated*, an oil painting on canvas by Igor V. Zaitsev. This painting was created for the May 12th International Awareness Day for Chronic Immunological and Neurological Diseases: Myalgic Encephalomyelitis, Chronic Fatigue Syndrome, Fibromyalgia, Gulf War Syndrome, and Multiple Chemical Sensitivity. These diseases affect both men and women, regardless of their race, nationality, and age.

that has been successful for many years. Connections between the arts and sciences are important to attract students' attention to problems they might not experience themselves. As some students indicated, socioeconomic factors should be taken into consideration when statistics are used in clinical studies.

○ Conclusion

The case study presented here uses a controversial human disease as an example to enhance students' learning in human body systems, symptoms of a disease, complexity of diagnosis, and the scientific method. It provides opportunities for students to build critical-thinking skills and interests in medical research studies. We introduced the case study to students who intended to pursue careers in health-related fields and they found it interesting and engaging. As shown in an earlier article (Zaitsev, 2009b), during such discussions we observed a high level of student participation and involvement, which not only increased their knowledge on the scientific approaches but also improved their skills of interaction and communication with each other. However, in the future we would modify the case study on the basis of feedback from students. As noted above, at the end of the activities half of our students believed that CFS/ME is a real disease while the others did not. Therefore, it is a great case study for creating a debate in the classroom. The debate should take place after the students' presentations. Alternatively, an essay on whether CFS/ME is a real disease could be assigned to each student. Perhaps those modifications may improve students' comprehension of the material.

○ Acknowledgments

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