Summary of the Viruses in Chronic Fatigue Syndrome & Post-Viral Fatigue Conference

The Viruses in Chronic Fatigue Syndrome & Post-Viral Fatigue Conference was held in Baltimore, Maryland, on June 22-23, 2008. Investigators from around the world examined evidence for the possible role of several different viruses in initiating and perpetuating chronic fatigue syndrome (CFS).

Post-Infectious Fatigue Syndrome (PIFS)

For over 60 years, scientists have reported sporadic cases of a chronic fatiguing illness developing in the wake of a well-documented infection. Nevertheless, it is only in the last few years that scientists have systematically studied this PIFS. These studies have begun by identifying all cases of a well-documented type of infection in a large group of people. Then, the research team carefully follows the patients for a long time thereafter, evaluating symptoms, and performing physical examinations and laboratory testing.

In 2006, a landmark study of post-infectious fatigue syndrome that was conducted in Dubbo, Australia, was published. The team studied people with each of three different kinds of infections—Epstein-Barr virus infection, Ross River virus infection, and infection with a bacterium, *Coxiella burnetii*, the cause of a disease called Q fever. The study showed that about 10% of patients in each of the three groups developed a post-infectious fatigue syndrome that met the Centers for Disease Control and Prevention (CDC) criteria for CFS.

At the Conference, the team reported in detail on this study. The chronic illness was most likely to develop in those patients who were sickest at the time of the initial infection: demographic, psychological and microbiological factors did not predict who would develop PIFS. Although final results were not presented, the team reported that the activity of a handful of genes predicted who would become most severely ill with PIFS, and that genes were plausible candidates to explain the symptoms of PIFS. In particular, the team found variations in the genes for two immune system chemicals that affect inflammation (cytokines)—interferon-γ and interleukin-10.

Human Herpesvirus-6 (HHV-6) and HHV-7

For almost 20 years, studies have found evidence associating HHV-6 with chronic fatigue syndrome (CFS). Most human beings are permanently infected with HHV-6, although the virus usually remains “asleep” (inactive) inside certain cells and is not making copies of itself. However, sometimes the virus “reawakens” and begins to multiply—a condition called active infection.

Any human being with an inactive infection—which is to say, most human beings—will have detectable antibodies against the virus in their blood. People with active infections can be identified by tests of antibodies, virus antigens, and viral nucleic acids in the blood. Most researchers who have studied it report that patients with CFS more often have active infection with HHV-6 than either healthy people or people with other illnesses than can cause fatigue.
At the Barcelona Conference in 2006, a preliminary study reported that patients with CFS and evidence of active infection with HHV-6 and/or a related virus, Epstein-Barr virus, improved when treated with an antiviral drug, valganciclovir (Valcyte®). However, that study did not give some patients the antiviral drug and other patients a placebo (i.e., sugar pill), and so it could not prove that the treatment actually helped. At the Baltimore Conference, the same group from Stanford University reported on a randomized, placebo-controlled trial. The study had ended just before the conference began, and only a small amount of the data had been analyzed. The patients who received the valganciclovir seemed to improve more than the patients given placebo, but further analysis of the data is required to determine the results of the study.

A team from Latvia reported that latent (inactive) infection with HHV-7 was present more often in patients with CFS than in healthy control subjects. The team also found that active infection with HHV-6 was present in many more patients with CFS than in healthy control subjects.

Epstein-Barr Virus

In the mid-1980’s, some cases of (what came to be called) CFS were associated with reactivated Epstein-Barr virus (EBV) infection.

At the Baltimore Conference, one team reported that a protein made by EBV during active infection stimulates the production of several cytokines. These cytokines can produce many of the symptoms of CFS. The team reported that the mechanism by which EBV induces the production of these cytokines is through triggering an immune system “master switch” called NF-κB.

Parvovirus

PIFS following infection with parvovirus B19 has been reported for more than a decade. A team from Japan followed over 200 patients immediately after they had been infected with the virus. PIFS was not associated with continued presence of viral DNA in the blood, but levels of complement—proteins involved in inflammation—were.

Another study found that people experiencing a lot of stress at the time they developed a new infection with parvovirus were more likely to go on to develop a PIFS that met criteria for CFS. In addition, as was found in the Dubbo study (above), patients whose immune system cells produced high levels of inflammatory cytokines at the time of initial infection were also more likely to go on to develop a PIFS.

Enteroviruses

Enteroviruses include three families of human viruses: Coxsackievirus, echovirus and poliovirus. These viruses can infect the cells of the brain and spinal cord, respiratory tract, muscle and gut cells, and have been suspected as a possible cause of CFS for many decades.

A research team reported finding enterovirus RNA (viral genetic material) and high levels of antibodies against enteroviruses more often in patients with CFS than in healthy control subjects. Stomach biopsies were performed in some patients with CFS who had abdominal symptoms: enterovirus antigens were found much more often in their stomach tissue than in stomach tissue.
from patients who had biopsies for reasons other than CFS (like possible stomach ulcers). In patients with enterovirus antigens in the stomach, enterovirus RNA was also found.

**Borna disease virus**

Borna disease virus has long been recognized to infect animals that are in close contact with humans—horses, cattle, dogs and cats. It causes infection of the brain, particularly the limbic system, which is involved in emotion, behavior, and long-term memory. A team from Germany reported the latest research from its laboratory indicating that the virus also can infect humans, and may cause various mood disorders.

The team reported that it had isolated Borna disease virus from the blood of a U.S. patient with CFS. In the test tube, they found that the virus was killed by an antiviral drug called amantadine. They then found that a German patient with CFS and evidence of Borna disease virus infection improved clinically with amantadine treatment.

A team from Japan reported finding evidence of Borna disease virus in about 10% of patients with CFS.

**Endogenous retroviruses**

Nested among each of our genes are sequences of DNA that may make viruses called endogenous retroviruses. These DNA segments have been inherited from our parents, and entered the human genome millions of years ago. Most of them are thought to be unable to actually make retroviruses.

One research team reported that a particular endogenous retrovirus called human endogenous retrovirus-K18 (HERV-K18) can be induced to make viruses when a cell is infected with Epstein-Barr virus or stimulated by a chemical called interferon-α (which is both a natural chemical and a drug used to treat various diseases). Three different variants of HERV-K18 exist. The team reported that one variant, K18.3, is found more often in patients with CFS.

The possibility that HERV-K18 might trigger CFS in some people is plausible: HERV-K18 makes a protein called a “superantigen” that triggers a strong immune response and dysregulates the immune system. Such a response could theoretically trigger the symptoms of CFS. This research is preliminary, but intriguing.

**Immunological and genetic studies**

*Gene polymorphisms.* Contemporary biology allows scientists to do something that was impossible only 30 years ago: to easily identify gene variations. Some genes exist in several subtly different forms, called polymorphisms. The polymorphisms were caused by a mutation, typically one that occurred in a distant ancestor and was passed on to future generations. Tiny mutations in a gene can change the function of the protein made by the gene, and that can lead to disease.

A team using genetic data collected by the CDC reported that several polymorphisms in genes that are part of the brain hormone system (“neuroendocrine system”) are found much more often in people with CFS. It is well known that the brain hormone system “talks” to the immune
system, through various chemical signals. The team showed that the communication between these two systems was quite different in patients with CFS than in healthy control subjects.

**Gene expression studies.** Contemporary biology also allows scientists to do something else that was impossible only 20 years ago: to identify every gene in a cell, and determine if it is turned on or off. Genes that are turned on are said to be “expressed”: they are making the protein that they were built to make. For example, scientists can take a group of cells—like white blood cells in patients with a particular disease, or diseased tissue (such as a particular type of cancer)—and see which of the roughly 22,000 human genes are being expressed, and which are not: a “gene expression fingerprint”.

A research team from England reported that 88 genes (out of the approximately 22,000 human genes) were uniquely expressed in the white blood cells of patients with CFS: 85 genes were turned on, and 3 were turned off. The 88 genes typically involved biological functions that are central to the immune response to infection—which is consistent with the idea that CFS can be triggered and/or perpetuated by certain infections.

**Immunological abnormalities and symptoms.** One presentation summarized the immunological measurements that distinguish patients with CFS from healthy controls, including: increased numbers of activated T cells (a type of white blood cell); impaired function of T cells and natural killer cells (NK cells), another type of white blood cell; Th2 cytokine shift (a change in the type of cytokines produced); increased levels and production of inflammatory cytokines; reduced amounts of a molecule called soluble CD26; and increased amounts of a molecule called NPY.

But did these measurable abnormalities have any connection to the symptoms that patients with CFS were experiencing? Data were presented indicating that diminished T cell and NK cell function correlate with cognitive impairment and reduced level of function.

**Summary**

CFS was named and defined only 20 years ago, although a similar illness had been described in the medical literature for hundreds of years. The possibility that CFS is often triggered by infectious agents has been widely discussed and debated. Few scientists have argued that a *single novel* infectious agent is responsible for CFS, in the way that HIV is the central and necessary cause of AIDS. Indeed, most illnesses caused by infectious agents can be caused by *multiple* different types of infectious agents. For example, bronchitis, gastroenteritis, hepatitis, urinary infections, and the common cold are each caused by multiple infectious agents.

This conference presented evidence that a handful of infectious agents are plausible triggers of CFS. The evidence was both direct—associations between an infectious agent and CFS—and indirect—evidence of an immune response in CFS that suggests the body may be attempting to battle an infectious agent.

Altogether, both proponents and opponents of the theory that CFS can be triggered by infectious agents had much food for thought.