

Why is one person able to recover from an infection that plunges another person into a chronic and often disabling illness? This is the question the Dubbo studies are attempting to answer.

The Infection Connection

BY CORT JOHNSON, GUEST CONTRIBUTOR

AT-A-GLANCE ►►

- The Dubbo studies followed a group of people with specific infections to investigate the potential onset of CFS.
- Study results showed that regardless of the initiating infection, about 12 percent of the subjects developed CFS.
- Further investigation uncovered subtle differences in the immune response of the subjects who ultimately developed CFS.

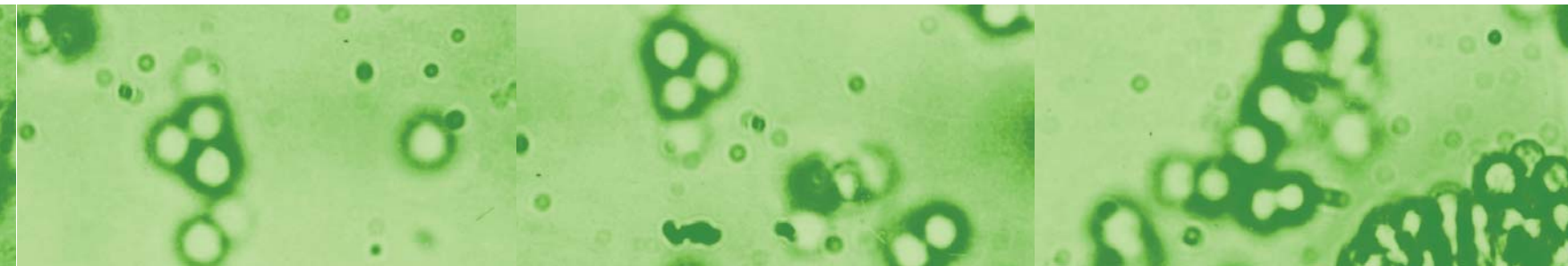
Almost all chronic fatigue syndrome (CFS) research studies examine CFS patients after they have come down with the illness. But the Dubbo studies—a CFS research project with multiple elements and a unique premise—are actually trying to catch the disease process in the act.

Various studies through the years have indicated that several serious infections may cause CFS in a certain percentage of people infected. Anecdotally, many people with CFS report an onset following an episode of infection. So the Dubbo study researchers, led by Dr. Andrew Lloyd of the University of New South Wales, set out to follow a group of infected people and investigate the course of illness, including any postinfective fatigue and possible CFS that results.

These studies, which are cosponsored by the Centers for Disease Control and Prevention (CDC) and the Australian government, have enlisted the help of 94 family practitioners in the rural township of Dubbo, Australia, to provide them with people who've become infected with Ross River virus (RRV), Epstein-Barr virus (EBV, infectious mononucleosis or glandular fever) or Q fever (caused by a bacterium *Coxiella burnetii*). So far 253 people have participated: 68 with EBV infection, 60 with Ross River virus, 43 with Q fever and 82 in which researchers weren't able to confirm the infection.

These patients were given detailed physical and psychiatric assessments and blood tests to determine their immune status and gene expression patterns. Investigators then evaluated each patient at three weeks, six weeks, three months, six months and one year after they were infected. All along they were monitored for postinfective fatigue, and at the six-month phase they were each assessed for CFS using the 1994 International Case Definition.

The results thus far have been fascinating. For one thing, the rates of CFS that appear to be caused by each pathogen are strikingly similar. About 12 percent of those infected by each pathogen end up meeting the criteria for CFS six months later. Their symptom presentation is very similar as well. Regardless of the specific symptoms of the initial infection, by the six-month mark all of the postinfective fatigue patients present essentially the same symptoms—those fitting the criteria for CFS.



These are remarkable findings. EBV, RRV and Q fever are, after all, very different pathogens. EBV is a DNA virus that targets B lymphocytes; Ross River virus is an RNA virus that targets the joints; and Q fever is not a virus at all, but a rickettsial bacteria. All affect the body in different ways, but ultimately all appear to cause the same type of chronic illness in some people. This suggests that it's not the pathogen *per se* that causes postinfectious CFS, but the body's response to infection in general.

Since these are infectious agents, the first place the researchers looked was the immune system. They wanted to explore two things: whether these patients were still sick because they'd been unable to fight off the invader, or whether they were sick because their immune systems had gone into overdrive in an attempt to do so.

An analysis focused specifically on the infectious EBV set of Dubbo patients suggested that neither explanation was true. In that study, it appeared that the patients successfully fought off the invader and had largely normal immune responses.

There were *some* abnormalities, however. The EBV patients who ended up coming down with CFS took a bit longer to rev up their immune response and a bit longer to fight the virus off. In addition, their antibody responses to the virus occurred earlier. Symptomatically,

they were also much sicker during the initial stage of the illness than the controls (those who got better after infection). Their rates of mood disorder were not significantly increased, however, and the Dubbo researchers dismissed psychological factors as a contributor to their illness.

Instead, they suggested these findings could reflect what some CFS researchers have long believed—that the immune systems of people with or prone to CFS are a bit out of balance. This could have been responsible for both the slight tardiness of the immune response and the early antibody response of the CFS patients in the study. The researchers proposed that the CFS patients might display increased production of an important anti-inflammatory immune messenger called interleukin-10 (IL-10).

The results from a follow-up Dubbo study suggested the earlier one was on the right track. At the 2007 International Association of CFS/ME (IACFS/ME) conference, Dr. Toni Whistler of the CDC reported that gene expression tests conducted over the course of a year found evidence of three immune abnormalities. Anti-inflammatory genes involved with IL-10 production appeared to be working overtime, while the genes producing the receptors on cells responsible for warning of a pathogen attack were strangely quiet. An important process designed to rid the body of infected cells—also known as cell

suicide or apoptosis—also appeared to be operating abnormally.

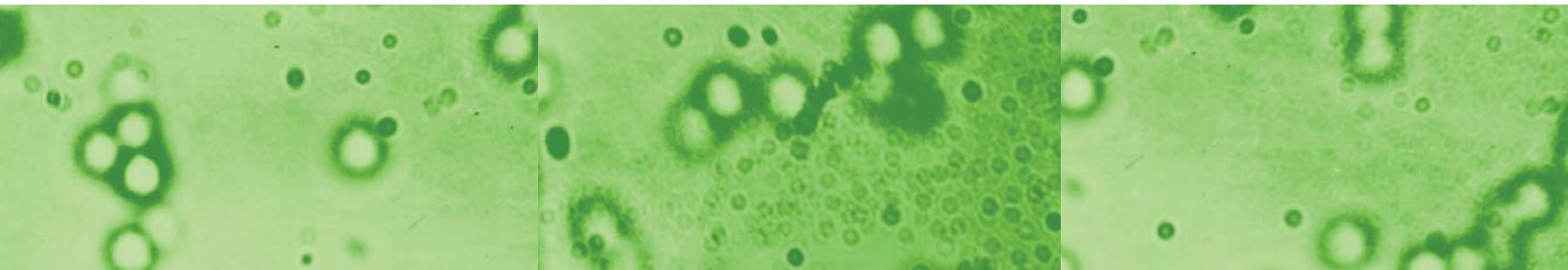
So it appears the CFS patients had difficulty in three basic aspects of the immune response: identifying the invader, mounting a strong attack against it and killing the cells it had infected.

Ultimately, though, while it took them a bit longer to do it, the CFS patients still appeared able to fight off the pathogens. As time went on their viral loads and antibody responses dropped just as happened in the control subjects without CFS.

So if the pathogen was gone, why were they still sick? Here researchers can only speculate.

One theory is that the slightly retarded immune response in the CFS patients allowed the pathogens to do more damage before they were eradicated. Dubbo researchers found that the primary predictor of CFS was the severity of the initiating acute illness. The more severe symptoms in the CFS patients suggest to Dr. Lloyd that nervous system damage occurring early in the infection may have affected parts of the brain involved in fatigue, cognition and other processes.

In some ways a central nervous system component would not be surprising. Researchers believe that many of the symptoms we associate with infection originate in the brain. Just as the pain caused by a wound stops us from moving a limb, many of the



uncomfortable symptoms we associate with infection appear to be intentionally produced by the brain in order to induce us to rest. Indeed the Dubbo researchers found that some of the symptoms associated with the early stages of infection did resolve in the CFS patients, but that others, such as fatigue and cognitive problems, remained. This suggests that some aspects of the central nervous system that become activated during infection may have become damaged in these CFS patients.

Dr. Lloyd isn't alone in believing that central nervous system damage plays a key role in CFS. The leader of the large Japanese effort on CFS, Dr. Hirohiko Kuratsune, presented a chart at the 2007 IACFS/ME conference positing that not only infection but toxins, injury and other types of physical as well as psychological stressors produce neural insults that dramatically reorder the way CFS patients' brains function. Dr. Kuratsune believes that reduced activity in a part of the brain called the anterior cingulate is responsible for both the pain and fatigue found in fibromyalgia and CFS. Recent CFS brain imaging studies suggest that several parts of the brain involved in energy production, concentration, mood and sleep are altered in CFS patients. A similar scenario appears to apply to fibromyalgia, a disease with many ties to CFS that can also be triggered by infection.

Despite the Dubbo team's work in this area it's still not clear, however, that the pathogens have been eliminated in all postinfectious CFS patients. At the IACFS/ME conference, several preliminary studies reporting antiviral therapy can lead to improvement in a subset of CFS patients suggest that this subset may suffer from chronic, undiagnosed infections. Other studies presented at the conference suggest that rates of active HHV-6 and enteroviral infection are increased in CFS or that an unusual kind of EBV infection may be present. There may very well be different subsets within the larger postinfectious subset of CFS.

This is an exciting time for postinfectious CFS patients. An NIH-funded study by Dr. Renee Taylor, due to finish next year, is examining other biologic parameters of postinfectious disease in CFS

including natural killer (NK) cell function, salivary cortisol levels, ACTH and orthostatic intolerance. An antiviral drug trial studying the effects of Valcyte is under way under Dr. Jose Montoya's direction at Stanford University, and Dr. Jonathan Kerr in the U.K. is experimenting with the drug interferon-beta, which has antiviral and immunomodulatory properties. We're still in the early stages of understanding the postinfective disease process, but the work is at last gaining new momentum. ■

Cort Johnson runs the Phoenix Rising website, an online resource for stories, research briefings and interviews on the subject of CFS. Cort has a Masters degree in environmental studies and devotes much of his time to studying CFS research and medicine. <http://phoenix-cfs.org>

PROMISE DENIED?

Even promising projects like the Dubbo studies is not immune to funding woes. Dr. Lloyd, the leader of the Dubbo effort, has plans to analyze this intriguing patient group in great detail—examining genetics, gene expression, brain activity, the brain-muscle connection and more. But unfortunately and unexpectedly, the funding well has begun to run dry. The Dubbo study's major sponsor, the CFS research program at the CDC, now has funding challenges of its own and several attempts to receive grants from the NIH have failed.

We will hear more from the Dubbo studies—several papers are in the works—but unless Dr. Lloyd and his research colleagues can secure more funding this year, this unique project may soon end.