



CFS Research: Looking for a Breakthrough

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The body of evidence is building in the 20-year scientific investigation of CFS. How are established facts, new clues and advanced technology coming together to make an impact?

Crime shows have always enjoyed a certain popularity on television, from *Dagnet* to *Hill Street Blues* to *Law & Order*. These series focus on different aspects of the criminal justice system; some highlight the skills and temperament needed to solve crimes, while others emphasize cutting-edge forensic procedures that lead to convictions. I've spent the last 10 years of my career tracking a culprit of sorts: the biological underpinnings of CFS. My training as a microbiologist and experience with chronic viral diseases attracted me to the challenges posed by this illness. My colleagues across the globe in this scientific sleuthing have brought their expertise and instincts to bear, and we've all benefited from ever-improving technological advances that give us new tools for the hunt.

More than 20 years after the first definition for CFS was published, what can we say with confidence about this complex, disabling condition, and where are we headed?

Let's quantify the field first. Over the last two decades, more than 3,500 peer-reviewed articles have been published about CFS. Investigators from all over the world have made contributions, with the majority of work coming from groups in Australia, Europe, Great Britain, Japan and the United States. The United States government has spent about \$187 million on CFS research, and the CFIDS Association has supported an additional \$5 million in studies. Judging by attendance at the last conference of the International Association of CFS/ME (IACFS/ME) and other indicators, it appears that more scientists are studying CFS than ever before; however, the field still needs to grow in terms of numbers and types of expertise to decipher the complexities of CFS.

AT-A-GLANCE ►

- 20 years of study have yielded knowledge about CFS epidemiology and uncovered many clues about CFS biology.
- New investigative tools, like gene microarrays and bioinformatics, are extending the reach of CFS research—and some of the findings underscore earlier discoveries.
- The CFS research field is poised to accelerate progress toward identifying the biologic underpinnings of this illness.

Defining CFS was an important first step in 1987, even though there have been several case definitions since then, and the subject continues to generate debate. With a definition, researchers were able to begin studying the distribution and determinants of illness in specific populations—assessing the “crime” and who was harmed by it. The first studies focused on clusters of ill people (like those in the Incline Village, Nevada, and Lyndonville, New York, “outbreaks”) or clinic populations. Later, other studies looked at broader populations like Chicago, Wichita and Georgia.

From these efforts we’ve made significant progress describing the epidemiology of CFS, and we can now confidently state that CFS is a common and severely debilitating condition that affects more than one million Americans. Women are more likely to get CFS than men. Adults are at higher risk for CFS than teens, and teens get it more often than young children. Less than 20 percent of people with CFS have been diagnosed. The illness imposes great economic burdens on the individual, the family and the nation as a whole.

But what do we know about what CFS does to the body? Investigators, using the traditional tools of science to poke around numerous body systems, have piled up evidence of often-subtle abnormalities in the immune system, the brain, the hypothalamic-pituitary-adrenal (HPA) axis, the cardiovascular system, the autonomic nervous system and the endocrine system. Anthony Komaroff, MD, of Harvard Medical School elegantly summarized these abnormalities in an article published in the 2006 special edition *CFIDS Chronicle*, the *Science & Research of CFS*. These studies, often examining one variable at a time, have identified scores of “suspects” that might be implicated in CFS.

Over the past five years, completion of the Human Genome Project (see boxed story) has given us new technologies to survey the crime scene, helping focus our attention on the most likely suspects who had motive and opportunity, in addition to long rap sheets. Like the cutting-edge forensic tools the investigators on *CSI* employ to solve crimes, we’ve used genomics, proteomics and gene microarrays to understand what’s going on at a molecular level in CFS patients. Now, rather than running one blood test to get one result, a single blood sample

yields millions of pieces of information about possible genetic variations and the state of thousands of gene expression patterns and proteins. Additionally, bioinformatics (computational study) has allowed us to examine large complex data sets and to identify patterns linking findings that would have been nearly impossible to see using only traditional data analysis techniques.

In investigative terms, we’ve narrowed the suspect list and implicated some key participants in this illness, but we’re still searching to find the primary culprit behind all the damage being done.

After 20 years we still don’t have definitive telltale physical signs, accessible anatomical lesions or readily measured biological markers for CFS, but the two paths of investigation—traditional and molecular—have converged on some important and promising discoveries. For instance, some of the early studies of CFS pointed to atypical levels and responses associated with several chemical messengers called neurotransmitters—such as serotonin¹⁻³ and catecholamines⁴⁻⁵—that help regulate sleep, body temperature, heart rate, appetite, mood and immune function. These early and astute observations underscore the findings of recent genetic studies. There is now evidence that genes involved in the function of serotonergic, dopaminergic and catecholaminergic systems display unusual sequences in people with CFS. These unusual sequences, known as polymorphisms, are not likely to cause CFS, but they might make people more vulnerable to the illness. This both helps support the earlier findings of abnormal levels of some neurotransmitters and helps focus future investigations to understand what they might mean.

Linking molecular data to clinical information about characteristics CFS patients display in sleep studies, stress tests and functional imaging studies will accelerate what we know about CFS in general and under various conditions. It may also help us “sort” CFS into different subtypes, as four teams of researchers did during the C3 challenge I led while at the CDC; and as Jonathan Kerr, MD, PhD, and a team of United Kingdom researchers recently reported in their own study⁶ (see page 4). These approaches can also help refine our understanding about sets of individuals with similar CFS profiles rather than trying to understand a very diverse patient group all at once.

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The convergence of these research paths is also helping us understand the key contributions of both genes and the environment in CFS. We're taught in high school biology that our genes determine some aspects of who we are and how we look—our sex, eye color, height, etc. But our genes face an ongoing barrage of challenges from our environment that ultimately determine who we become. Nature and nurture combine to influence events as basic as how we digest various foods to processes as complex as how we weather personal crises. CFS is probably influenced by the interaction of our genes with our environment as well.

One of the most fascinating areas of research where this dynamic can be observed is in infection. From the very beginning, clues pointed to at least a subset of CFS that

follows infection. In fact, CFS was initially thought to be a chronic form of mononucleosis and was associated with Epstein-Barr virus (EBV). That trail went dead for a while when not every case of CFS could be linked to EBV (or other viruses that were studied), but new tools are focusing on gaining a better understanding of what happens when people don't recover from certain viral and bacterial infections, and symptoms consistent with CFS persist well beyond the usual period of acute illness. One study by Andrew Lloyd, MD, and his colleagues found that 10 percent of people who became infected with one of three very different agents—EBV, Ross River virus and Q fever—remained ill for months after the other 90 percent had recovered⁷. The

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IN SCIENTIFIC TERMS

The Human Genome Project is an international research effort to sequence and map all of the genes—together known as the genome—of the human species. Completed in April 2003, it created the ability to read the complete genetic blueprint for a human being.

A substance known as **DNA** makes up the genome of all living creatures. DNA is formed by an “alphabet” of specific sequences that spell “words,” or genes. Just as variations in the spelling of a word affect its meaning, in the case of genes, different sequences can affect the gene's function. These sequence variations, called **polymorphisms**, can be used to distinguish groups of people. **Genomics** is the study of genes and their functions.

The action of genes as they turn on and off in response to internal and external stimuli is called **gene expression**. Molecular technologies, including **gene chips** and **microarrays**, allow us to measure gene expression activity and to use this information to separate people into biologically meaningful groups.

Proteomics is the study of the structure, function and interaction of proteins produced by genes in cells, tissues or organisms. Proteins can take the form of **enzymes** and **antibodies** that play specific roles in the body's healthy functioning.

severity of the initial infection was a key predictor for who stayed sick and who got better, and studies continue in search of genetic or gene expression factors that may also separate the two groups.

We also know from studies performed at the CDC and by Kerr and other groups that CFS patients demonstrate disturbed gene expression patterns in several different “compartments” of the immune system. These differences might play a role in how individuals respond to infection.

In a cutting-edge paper in the prestigious *Journal of Immunology*, Dr. Brigitte Huber, PhD, demonstrated that EBV affects T cell activity (part of the body’s immune defense mechanism) by initiating expression of the HERV-K18 env gene⁸. Now, in a pilot study using funds provided by the CFIDS Association, Huber has found preliminary evidence that the HERV-K18 env gene may be a risk factor for the subtype of CFS that follows EBV infection. She’ll follow her pilot research with a larger scale study funded by NIH.

Evidence like this suggests that one form of CFS may arise from certain genetic vulnerabilities challenged by particularly severe infections under conditions that prevent the body from returning to homeostasis. Science is beginning to reveal the biologic underpinnings of this illness.

With as much as we’ve learned about CFS over the past 20 years, we now have an opportunity to integrate data and harness this knowledge in new and powerful ways. By focusing on abnormalities that show up using both traditional methods and newer ones—and for which the evidence is supported by lab and clinical studies—we can greatly accelerate the pace of progress in identifying biologic indicators of CFS. This will aid early detection, objective diagnosis and effective treatment.

It won’t be simple. We’ll need to forge new partnerships, strengthen collaborations among investigators and tap other areas of expertise to overcome the scientific, political and funding barriers still ahead. However, we’re better positioned to do so than ever before. As a disease detective, it feels as though credible informants, effective questioning methods, clear forensic evidence and dogged determination may soon yield that crack in the case we’ve all been working toward. ■

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