The Massachusetts CFIDS/ME & FM Association held its Fall 2011 educational forum, co-sponsored by the Massachusetts Department of Health, on November 5, 2011 at the UMass-Hinton State Laboratory Institute Auditorium in Jamaica Plain, MA. Review of research abstracts from the September 2011 International Association for Chronic Fatigue Syndrome /Myalgic Encephalomyelitis (IACFS/ME) Conference held in Ottawa, Canada was presented in two segments: Dr. Anthony Komaroff's review of the conference highlights (on audio, with accompanying slides), while Dr. Kenneth Friedman and Dr. Alan Gurwitt spoke about other studies, news and developments (their presentation will be released as a separate article, due to the length and depth of content).

As always, Dr. Komaroff's summary of the IACFS/ME meeting highlights was most informative and articulate, and the Massachusetts CFIDS/ME & FM Association is deeply appreciative of Dr. Komaroff's continued interest and support of our educational programs in giving us permission to replay this material.

The following article reviews studies selected by Dr. Komaroff which he felt had represented some of the more intriguing and provocative areas of research, as listed:

Epidemiology

A long-term study done by Dr. Leonard Jason, from DePaul University in Chicago IL, helps to answer the question of what is the longer term history of CFS. Data gathered for 213 patients, over a period of 15 years or longer, showed that 67% of individuals continued to fit CFS criteria; some who initially had idiopathic chronic fatigue, went on to develop full-blown CFS; and half of those who no longer had CFS, still had fatigue. Dr. Komaroff explained this suggests there is a continuum between full-blown CFS, idiopathic chronic fatigue, and normal health. Thus over time, some patients move back and forth between these categories. This study confirms that CFS is a chronic illness and in adults, it can persist for decades.

Two studies conducted by Dr. Elizabeth Unger, from the Centers for Disease Control and Prevention (CDC), show improvement in the overall recognition of CFS by the medical community and general public over the past 20 years. The first study focused on health care practitioners. Of the 2,000 surveyed, the majority of them (94%) had heard of CFS; 37% reported they had personally diagnosed cases of CFS in their practice; and about 14% of them

still thought CFS was a psychiatric condition. The second study surveyed 4,200 U.S. citizens. More than of half (57%) reported they had heard of CFS, while only 2% of the public still believed it was a psychiatric condition. Dr. Komaroff said that when thinking back to the first international CFS conference held in 1992, this data demonstrates substantial change in awareness and knowledge of CFS.

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Virology

One of the poster presentations made by Dr. John Chia and his son, Andrew Chia, demonstrated that enteroviral infections were frequently found in CFS. Their research confirmed enteroviruses (EV) in the tissue samples taken from 132 consecutive stomach biopsies of CFS patients. (Some of these patients also had gastrointestinal symptoms). The majority of CFS cases tested positive— 82% had viral protein and 64% had viral nucleic acid, while EV was found in only a small fraction of controls (i.e., 10% or 4 of 40 controls). In addition, when biopsied material that looked like it contained viral antigens and proteins was injected into animals which were later checked for replicating virus, many of them revealed production of antiviral proteins and antibodies to the EV. The importance of this study, according to Dr. Komaroff, was that the Chias' research suggests EV may play a central role in this illness.

Topics of utmost interest at the Ottawa conference were xenotropic murine leukemia retroviruses (XMRV) and polytropic murine leukemia viruses (pMLVs), especially since the results of the multi-laboratory XMRV/MLV study were being published by Science journal at the same time. Dr. Komaroff briefly touched on the differences in research findings, from the original data published by Whittemore Peterson Institute (WPI) to the final results of the Blood Working Group Study. Two years ago, WPI came out with some remarkable information: a significant percentage of CFS patients were found to have viral nucleic acid and viral antigen to XMRV; that the virus could be cultivated from patients' plasma and cells; that antibodies to the virus were found in CFS patients; and moreover, that some of the healthy blood donors had also tested positive. A second study by scientists from the National Institutes of Health (NIH) and Food and Drug Administration (FDA) only looked for XMRV viral nucleic acid, which they failed to confirm. However, they detected MLV-related virus in CFS. Many laboratories around the world tried to repeat the studies, but results came back negative and/or with inconsistencies. A large replication study was established to verify these findings. The research was spread across 9 highly reputable laboratories that conducted blinded testing of blood samples from a large CFS patient group, including those which had previously tested positive for XMRV or pMLVs. But the results were negative.

False positives of XMRV /pMLVs are now attributed to contamination of laboratory reagents and commercial reagents with mouse DNA. Dr. Komaroff indicated that XMRV was an accidental laboratory recombinant virus, going back to the early 1990s and considered this finding in itself as troubling, because quite a few people developed CFS many years prior to this incident. Various cell lines were also found to be contaminated with mouse DNA and this contamination is considered to be widespread, affecting many laboratories around the world. In view of these results and developments, Dr. Komaroff regards XMRV/ pMLVS research to be on very “shaky grounds.” Links to more information about XMRV developments and the Science journal that published results of the multi-lab study are provided at the end of this article.

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Immunology

Most previous studies on Natural Killer (NK) cell function had shown reduced function in CFS patients. However, two studies presented at the Ottawa conference came to two different conclusions. One study confirmed impaired NK cell function in CFS/ME patients which may be related to alterations in cytokines and reduced immune function in patients with CFS (EW Brenu). The other study found that NK cell function was higher in patients while they were acutely ill and during a period of time following the active infection (B Katz). Dr. Komaroff thought this was quite feasible because if a viral infection is believed to trigger this illness, which applies to many but not all cases, then NK cell function could increase during the initial phase of infection and remain relatively stable, for a while, immediately after an infection. But when patients become chronically ill and NK cells are repeatedly activated to protect the body against viruses and other pathogens, this could lead to an exhaustion of NK cell function response (i.e., what is commonly seen in full-blown, persistent CFS).

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Exercise challenge studies

An exercise challenge study is actually a set of maximum exercise tests (i.e., in this case, not an elaborate technique, but a commonly used test in clinical settings for decades) that is conducted 24 hours apart and can measure post-exertional malaise. Dr. Komaroff regards work done by Betsy Keller in this field to be provocative and valuable because it is able to demonstrate significant changes between the first and second exercise tests, such as decreased work capacity, decreased heart rate, lower anaerobic threshold and lower functional capacity. After the second test, post-exertional malaise brought significantly reduced functional capacity—below that which would be typically needed for many sedentary jobs and daily living

activities. Exercise challenge tests, in Dr. Komaroff's opinion, suggest a way that post-exertional malaise could be documented for a variety of needs.

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Studies of the brain

Dr. Komaroff remarked that many interesting studies of the brain were presented at the conference, even though he did not go into too much detail on these. Some of the many brain abnormalities included reductions in grey matter and white matter (IH Treasaden) and decreased activation of basal ganglia (i.e., typically in the caudate and globus pallidus) in CFS and other fatiguing, neurological illnesses using advanced functional magnetic resonance (fMRI) techniques (AH Miller). Other remarkable research alluded to by Dr. Miller (not part of the abstracts presented at the conference) was the ability to experimentally induce fatigue and reduce activation in basal ganglia, in humans, with the infusion of pro-inflammatory cytokines. Symptoms of CFS have long been associated with pro-inflammatory cytokines produced in, or getting through the brain blood-barrier, and into the central nervous system.

Another study of the brain assessed blood flow in patients with CFS, those with major depressive disorder, and healthy controls. Cerebral blood flow to certain regions of the brain was notably reduced in CFS when compared to healthy controls and no significant differences were found in values between CFS and major depressive disorder (JP Dyke). Though this pilot study was felt to be intriguing, Dr. Komaroff said it needs to be reproduced, because a small study like this is prone to the beta error problem (i.e., the problem in finding real differences in small studies is difficult). The measurement of tissue blood flow in the brain has greatly advanced, and this technology is now widely available and may allow for better assessment and treatment of patients. But how this technology will be ultimately used needs to be worked out.

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Gene structure and expression

Do people with CFS have differences in the way their genes are built—from inheritance—compared to health controls? Is there a difference in which genes are "turned on" (expressed)? Is there a relationship between these differences and the underlying biology of this illness?

Dr. Komaroff reviewed a selection of genomic and genetic research presentations from the Ottawa conference which exemplify how this science and tools can help to identify patterns unique to CFS. It is important to note many other fields are using gene expression patterns/results in their studies to evaluate CFS compared to healthy controls or other illnesses.

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Gene structure

Gene structure in CFS was assessed by Dr. M.S. Rajeevan, with the CDC, by using community-based samples and comparing these to healthy controls. This study reported polymorphisms in genes that are involved in the immune response—more specifically, complement cascade, chemokine production and toll-like receptor signaling—which were different in CFS patients. Basically, this study demonstrates how changes in gene sequences detected could determine that these genes played a role in innate immune response.

Dr. Lea Steele, at Baylor University, combined an epidemiological study with molecular biology, and identified two polymorphisms that reduced the body's ability to degrade nerve gases and pesticides, respectively. These polymorphisms were found to correlate strongly with the presence of Gulf War Syndrome in individuals who had been military personnel exposed to those environmental toxins, and not in those unexposed. Steele's study also showed a dose-response relationship with homozygotes of these polymorphisms had a clearer, more severe form of GWS compared to heterozygotes (per Dr. Komaroff's IACFS/ME Meeting Highlights PowerPoint slides on Gene Structure). Dr. Komaroff remarked that it remains to be seen whether these results in GWS will have any relevance to CFS/ME or Fibromyalgia.

A mini primer on gene expression, prepared by Dr. Komaroff, was helpful in getting across the basic aspects of this science, in this way:

Genes are only important if they are "expressed", or "turned on" and are making messenger RNA. The central process can be stated as follows: DNA -> makes messenger-RNA (mRNA) -> makes Protein. DNA not only makes full-length genes but also makes tiny microRNAs, which feed back on specific mRNAS and interfere with protein production. Consequently, they block protein production—the result is they "turn off" the gene.

A method of detecting gene expression is using a tool called microarrays, which allow for extensive analysis of many genes at one time (up to 22,000). This technique makes it possible to take a tissue and be able to tell which genes are turned on and off. Microarray tests are performed on silicone chips, and when a gene sequence finds its complementary match on the chip (when there is a fit), they will light up—the patterns of genes that are “turned on” help to make many inferences about what is going on.

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Gene Expression

The importance of gene expression can be demonstrated in this preliminary study that had found 6 miRNAs to be substantially down-regulated in both NK cells and CD8+ cells in CFS patients, compared to healthy controls. These cells play a critical role in antiviral activities and have been shown to function defectively in CFS in previous studies. These miRNAs regulate the expression of genes involved in cell cycle regulation, apoptosis, and toll-like receptor expression (EW Brenu).

An exercise challenge test, conducted at University of Miami, confirmed an enhanced alteration in the expression patterns of a group of genes, as previously found in ME/CFS by Dr. John Kerr from the U.K. (i.e, the Miami study used the Kerr ME/CFS platform to evaluate gene expressions). The genes that were altered are those which play important roles in antiviral defense, mitochondrial function, and immune activation. The same changes were not seen in healthy controls or patients with Gulf War Illness. (L Garcia)

Dr. G. Broderick used data from Dr. Katz’s study of adolescents with infectious mononucleosis and post-mono CFS, and his study could identify biological pathways that are up-regulated or down-regulated. Children with post-mono CFS had 5 signaling pathways with altered activity, most notably, the phenylalanine metabolic pathway which was down-regulated. Patients with greater down-regulation had greater fatigue—a “dose-response” relationship (Broderick, Katz, Taylor).

Dr. Lucinda Bateman presented research done by Dr. Alan Light and Dr. Kathleen Light that looked for changes that exercise would make in gene expressions, in patients with CFS, CFS and Fibromyalgia (FM), FM only, Multiple Sclerosis (MS), and in healthy controls. (CFS and FM patients used in this study were referred by Dr. Bateman, clinical collaborator.) Dr. Bateman

reported that both patient self-rated and physician-rated symptom severity correlated with greater post-exercise increases in these genes. However, a subgroup (about 30%) of patients did not demonstrate such gene expression changes and the clinical clue for difference was the history of orthostatic intolerance in this subgroup. Results seen in CFS patients were not seen in healthy controls, FM only, or MS.

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CFS multi-center research initiatives

The good news is there is a movement by key federal health agencies and other facilities/organizations, to better coordinate and collaborate research efforts, as shown below:

- CFIDS Association clinical and laboratory database
- NIH-funded multi-center study, centered at Columbia University
- CASA—Initiative of the NIH and CDC to develop common instruments and strategies for multicenter CFS research studies
- Chronic Fatigue Initiative—Multicenter initiative to discover possible pathogens and mechanisms of disease

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More Resources

View all abstracts of all IACFSME 2011 scientific papers presented at the presented at the IACFSME Biennial International Conference held in Ottawa, Canada on September 22-25, 2011. It is important to note that research presented over the course of the 4-day long Ottawa conference was extensive and the majority of it, highly technical.

For more information about recent and previous developments surrounding XRMV, please see the following links:

XMRV Not Found in Blood Working Group Study The multi-laboratory study results published in the journal Science of September 22, 2011

XMRV Update Links providing a very comprehensive timeline and overall picture of XMRV

research