



CHRONIC FATIGUE SYNDROME ADVISORY COMMITTEE

Meeting

Thursday, October 29, 2009
9:00 a.m. to 5:00 p.m.

Friday, October 30, 2009
9:00 a.m. to 4:00 p.m.

Room 800, Hubert H. Humphrey Building
200 Independence Avenue, SW
Washington, DC 20201

Agenda Thursday, October 29, 2009

9:00 a.m.	<u>Call to Order</u> <u>Opening Remarks</u>	pg 6	Dr. James Oleske <i>Chair, CFSAC</i>
	<u>Roll Call, Housekeeping</u>	pg 6	Dr. Wanda Jones <i>Designated Federal Official</i>
9:15 a.m.	<u>Agency Updates: Health Resources and Services Administration</u>	pg 37	<i>Ex-Officio Representatives</i>
	<u>Social Security Administration, National Institutes of Health, Food and Drug Administration, and the Centers for Disease Control and Prevention</u>	pg 7	
10:15 a.m.	<u>Presentation: XMRV Association with CFS</u>	pg 13	Dr. Daniel Peterson <i>Whittemore Peterson Institute, Reno, NV</i>
	<u>Presentation: Perspectives on XMRV and Related Retroviruses</u>	Pg 15	Dr. John Coffin, Principal Investigator, <i>Tufts University</i>
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12:15 p.m.	<u>Public Comments</u>	pg 18	Public
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9:00 a.m.	<u>Call to Order</u> <u>Opening Remarks</u>	pg 37	Dr. James Oleske <i>Chair, CFSAC</i>
	<u>Roll Call, Housekeeping</u>	pg 37	Dr. Wanda Jones <i>Designated Federal Official</i>
9:15 a.m.	<u>Public Comments</u>	pg 41	Public
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CHRONIC FATIGUE SYNDROME ADVISORY COMMITTEE

Voting Members

Chair

James M. Oleske, MD, MPH, CIP Term: 01/03/06 to 01/03/10
Newark, NJ

Rebecca Artman Term: 01/03/06 to 01/03/10
Middleburg, FL

Lucinda Bateman, MD, PC Term: 01/03/06 to 01/03/10
Salt Lake City, UT

Ronald Glaser, PhD Term: 04/01/07 to 04/01/11
Columbus, OH

Arthur J. Hartz, MD, PhD Term: 04/01/07 to 04/01/11
Iowa City, IA

Kristine Healy, MPH, PA-C Term: 01/03/06 to 01/03/10
Chicago, IL

Leonard Jason, PhD Term: 04/01/07 to 04/01/11
Chicago, IL

Nancy Klimas, MD Term: 04/01/07 to 04/01/11
Miami, FL

Jason Newfield, Esq. Term: 07/01/06 to 07/01/10
Garden City, NJ

Morris Papernik, MD Term: 01/03/06 to 01/03/10
Glastonbury, CT

Christopher Snell, PhD Term: 04/01/07 to 04/01/11
Stockton, CA

Ex Officio Members

Centers for Disease Control and Prevention (CDC)

J. Michael Miller, PhD (*Primary*)
Associate Director for Science
National Center for Zoonotic, Vector-borne, and Enteric Diseases

Ermias Belay, MD (*Alternate*)
Associate Director for Epidemiologic Science; Division of Viral and Rickettsial
Diseases; National Center for Zoonotic, Vector-borne, and Enteric Diseases

Food and Drug Administration (FDA)

Marc W. Cavaille-Coll, MD, PhD
Medical Officer Team Leader
Division of Special Pathogens and Immunologic Drug Products

Health Resources and Services Administration (HRSA)

Deborah Willis-Fillinger, MD (*Primary*)
Senior Medical Advisor
Office of the Administrator
Center for Quality

National Institutes of Health (NIH)

Eleanor Hanna, PhD
Associate Director for Special Projects and Centers
Office of Research on Women's Health

Social Security Administration (SSA)

Cheryl A. Williams (*Primary*)
Acting Director
Office of Medical Listings Improvement

Mike O'Connor (*Alternate*)
Supervisory Team Leader
Office of Medical Listings Improvement

Executive Secretary (Designated Federal Official)

Wanda K. Jones, DrPH

Deputy Assistant Secretary for Health (Women's Health)
Director, Office on Women's Health

Thursday, October 29, 2009

The following document contains highlights of the Chronic Fatigue Syndrome Advisory Committee (CFSAC) Meeting held on October 29-30, 2009. Access a pod cast of complete meeting proceedings at: <http://www.hhs.gov/advcomcfs/>.

Call to Order/Opening Remarks

Dr. Wanda Jones

- Welcomed attendees to the Great Hall of the Hubert H. Humphrey building where CFSAC web casts have the advantages of more space, more video cameras, better lighting, and better sound.
- Noted that cameras are focused mainly on CFSAC members and presenters, but asked to be notified if any audience members did not want to inadvertently appear on camera.

Dr. James Oleske

- Welcomed meeting attendees, particularly those representing patients and their families.
- Emphasized CFSAC's mission to develop recommendations that will help every patient and family cope with CFS and receive the health and human services to which Hubert Humphrey was committed. Dr. Oleske noted that the three CFSAC subcommittees had met since the full committee's May 2009 meeting to draw up recommendations that will improve the lives of Americans nationwide.
- Highlighted recent scientific discoveries and expressed hope that they lead to uncovering the causes of CFS.
- Noted that this was his last meeting as CFSAC chair, a position he has held for three years. Dr. Oleske thanked committee members and CFS patients and their families. While their testimony is moving and frustrating to hear, it has provided the energy and inspiration to carry on CFSAC's mission, said Dr. Oleske.

Roll Call, Housekeeping

Dr. Wanda Jones

- Noted that the web cast of the May 2009 CFSAC meeting attracted more than 100 views on day one, 70 views on day two, and hundreds of downloads.
- Conducted roll call with the following results: Dr. Glaser was absent; Dr. Deborah Willis-Fillinger, *ex officio* member representing the Health Resources and Services Administration (HRSA), would arrive later in the day; and *ex officio* alternate Mike O'Connor would represent the Social Security Administration (SSA).
- Noted that audience members must be escorted throughout the building and that water and a rest area were available at the back of the meeting room.
- Made the following agenda changes: added a presentation before lunch, moved the Subcommittee Lunch to 1:15 pm, and moved HRSA's agency update to the following morning.

Agency Updates

Mike O'Connor, Supervisory Team Leader, *Office of Medical Listings Improvement, SSA*

Mr. O'Connor introduced Joanna Marashlian, a social insurance specialist in the SSA Office of Disability Programs. Ms. Marashlian briefed CFSAC on how self employment is evaluated for **substantial gainful activity (SGA)** and provided an update on Ticket to Work and other SSA work incentives:

- All information is posted at www.socialsecurity.gov.
- SSA defines disability as the inability to engage in any SGA because of a medically-determinable physical or mental impairment that is expected to result in death or that has lasted or is expected to last for a continuous period of not less than 12 months.
- SSA generally uses earnings guidelines to evaluate SGA using one of two methods:
 - The "countable income test" – An individual is considered to be engaging in SGA if his or her monthly countable earnings average more than \$980 in 2009 or \$1000 in 2010.
 - The "three tests" – An individual's SGA is calculated by factoring in the nature of services, monthly income, and the individual's work compared to those without a disability.

- Ticket to Work is a program for those who receive SSA benefits and want to work. The latest program information is available at 1-866-YOURTICKET, 1-866-833-2967 for TDD users, or www.socialsecurity.gov/work/aboutticket.html.
- Trial work period – SSA beneficiaries can continue to receive benefits during a nine month trial work period. Information about this and other work incentives is provided in the 2009 Red Book – A Summary Guide to Employment Supports for Individuals with Disabilities under the Social Security Disability Insurance and Supplemental Security Income Programs at www.socialsecurity.gov/redbook.

Mr. O'Connor

- SSA is updating Social Security Ruling (SSR) 99-2p, which contains agency policy on evaluating disability claims based on CFS. The agency is evaluating the signs and laboratory findings in the current SSR to determine if they are up to date based on current medical knowledge of CFS.
- SSA's backlog of disability cases is decreasing. For the first time since 1999, the agency has reduced the number of pending hearings—37,000 less than in FY 2008. Over the same period, the average processing time for a case dropped from 514 days to 491 days. These improvements were made despite a significant workload increase due to the recession. Initial claims climbed from about 2.6 million per year to 2.9 million in FY 2009. SSA predicted 3 million new claims in FY 2010.
- SSA hired 147 new Administrative Law Judges (ALJ's) and 850 support staff in FY 2009 and plans to hire 226 additional ALJ's in FY 2010.
- SSA opened three new National Hearing Centers in Albuquerque, NM; Baltimore, MD; and Chicago, IL. The agency has plans to open 14 new hearing offices and four satellite offices by the end of next year, with the first opening scheduled for Anchorage, AK.
- ALJ's have increased their case-per-day productivity for the last three years. They averaged 2.3 cases per day in FY 2009.

Electronic Claims Process

SSA has completed its conversion to an electronic claims process. Staff can now instantly access any electronic disability claim file in SSA's national system. This helps ensure consistency in policy application. Any state or regional differences should be eliminated under this system of cross-state and cross-regional reviews.

Committee Discussion

Dr. Oleske asked for the total number of CFS disability claims as well as how many are accepted and how many are turned down. Mr. O'Connor said that the initial allowance rate is close to 40 percent. Additional cases are approved at the reconsideration and hearing levels.

Dr. Jason noted that the Patient Care/Quality of Life Subcommittee has sent SSA a request for data on CFS cases and inquired whether the report would be available by the next CFSAC meeting. Dr. Jason also questioned whether 491 days are an acceptable amount of time to wait for a hearing. Mr. O'Connor replied that the subcommittee questions have been submitted to the appropriate offices for data collection. He repeated that the SSA Commissioner is working diligently to reduce the wait time for a hearing by opening new hearing offices and hiring new ALJs.

Dr. Bateman stated that as a clinician and patient advocate, she has never seen a CFS disability case approved before the administrative hearing stage. She asked Mr. O'Connor what CFSAC might do to get patients an earlier disability approval. He replied that adjudicators are trained to consider all impairments, so the best strategy is for a patient to provide as much detailed information as possible from medical records and details about daily living. Dr. Bateman countered that even when CFS patients provide well-documented information, they are not approved at the initial two levels. She asked that SSA provide specific information on what can be done to speed up approvals.

Dr. Oleske welcomed **Dr. Glaser** to the meeting.

Dr. Eleanor Hanna, Associate Director for Special Projects and Centers, Office of Research on Women's Health (ORWH), NIH

Links to the materials in Dr. Hanna's presentation will be provided on the CFSAC website.

- ORWH leads the Trans-NIH Working Group for CFS. This year ORWH teamed with the Chronic Fatigue and Immune Dysfunction Syndrome (CFIDS) Association for a second meeting of new CFS investigators at the Banbury Center. Thirty-six investigators presented their work and expressed enthusiasm for creating a network for CFS research collaboration.
- The push toward electronic medical recordkeeping has led NIH to inquire how much it would cost to create a wiki to enhance communication among both intramural and extramural researchers. Dr. Hanna hoped to report more details before the end of the year.
- NIH is currently funding 12 CFS grants on a wide variety of topics including the immune system, neurological subjects, hypertension, and markers.

- The National Heart, Lung, and Blood Institute (NHLBI) has prepared a handout on blood supply safety activities. The handout addresses NHLBI blood supply monitoring activities since 1989 through the retroviral epidemiology donor study, which is currently in its second phase (REDS-II). Any time a new virus such as XMRV (xenotropic murine leukemia virus-related virus) arises, NHLBI tests its prevalence in the blood supply from the general donor population. There is no current evidence that XMRV is blood borne, but testing continues.
- Dr. Hanna provided three more articles addressing blood transfusion risks and noted that the National Cancer Institute (NCI) is preparing a Q&A fact sheet for the agency website that will address blood safety concerns.

Committee Discussion

Ms. Artman asked for a direct answer about whether or not CFS patients should continue to give blood in light of recent research showing a link between CFS and XMRV. Dr. Hanna replied that it is not currently known whether or not XMRV is blood borne and presents a transfusion risk. **Dr. Snell** noted that the NCI director advised that potentially infected people should refrain from blood donation. Dr. Hanna explained that the statement was cautionary and that the choice to donate blood is up to the individual.

Dr. Jones explained that a process is in place at DHHS to assess potential blood supply contaminants and the department would be providing clear guidance in a few weeks. She said that if individuals have been tested for XMRV and know that they have it in their blood; they may need to withdraw themselves from blood donation until the department issues better guidance. She added that protection of the blood supply is a priority at DHHS. **Dr. Klimas** advised that since CFS patients already have a lowered blood volume, they should refrain from giving blood because donations might cause their illness to worsen.

On the subject of research, Dr. Klimas highlighted the fact that two years ago, NIH's CFS Request for Applications (RFA) doubled the number of research grants. She asked if the agency plans another CFS RFA. Dr. Hanna replied that NIH will revise and reissue an RFA during the next fiscal year that takes into account recent research breakthroughs. She added that NIH also has a standing program announcement issued every three years that is broad enough to include almost any kind of research, including CFS. Dr. Hanna encouraged CFS researchers to take advantage of special programs such as the Roadmap Initiative and the clinical trials mechanism at the National Institute on Allergy and Infectious Diseases (NIAID).

Dr. Jason asked how much CFS research funding is being provided this year and whether or not funding is stable, increasing, or decreasing. Dr. Hanna answered that anyone can access funding information by clicking on the "Reporter" function on NIH's home page. She explained that the budget is determined by the number of research

studies that have been submitted and funded. She emphasized the importance of continuing to submit innovative and high-quality grant applications.

Dr. Marc W. Cavaille-Coll, Medical Officer Team Leader, *Division of Special Pathogens and Immunologic Drug Products, FDA*

Dr. Cavaille-Coll updated CFSAC on two recent FDA developments:

1. **The FDA Task Force on Transparency.** The CFSAC website includes a link to information on the task force, which was formed on June 2, 2009 to develop recommendations for enhancing the transparency of agency operations. The task force is seeking public input about how the agency can better explain its operations, including enforcement actions and product approvals. Dr. Cavaille-Coll said that FDA will consider legislative and regulatory changes. Other issues to be explored include early communications about emerging safety issues concerning FDA-regulated products, disclosure of information about product applications that have been abandoned, and communication about agency decisions concerning pending product applications.

2. **Patient report outcomes in clinical trials.** Dr. Cavaille-Coll expressed hope that final guidance on this subject would be released by the next CFSAC meeting.

Committee Discussion

Dr. Klimas asked whether FDA plans to keep track of any adverse outcomes in the CFS population to the three drugs that won FDA approval for fibromyalgia (FM). Dr. Cavaille-Coll replied that drug companies must monitor new products, report safety issues, and continue to submit periodic reports throughout the lifetime of the product.

Dr. Jason asked Dr. Cavaille-Coll to comment on the length of time of the ongoing approval process for Ampligen in light of the fact that no FDA-approved drugs are available to treat CFS. Dr. Cavaille-Coll said that he is prevented by law from commenting on a pending FDA drug application. He added that FDA is committed to completing its Ampligen review as quickly as possible.

Dr. Papernik asked whether Ampligen could be considered an orphan drug. Dr. Cavaille-Coll said that Ampligen's sponsor has applied for and been granted an orphan drug designation from the Office of Orphan Drugs. This status allows the sponsor to write off certain drug development costs and confers seven years of exclusivity for the molecular entity for that indication. Fast tracking a drug is a separate issue, although it is expected that products receiving the orphan drug designation will also be considered for fast-track drug development designation. The FDA's Orange Book lists the year that products receive orphan drug designation as well as for what indication the designation was granted.

Dr. J. Michael Miller, Associate Director for Science, *National Center for Zoonotic, Vector-borne, and Enteric Diseases, CDC*

The revised CDC CFS Public Health Research Program five-year plan is posted on the CDC website. Revisions took into consideration the 2008 external peer review, the April 2009 public meeting, the May 2009 CFSAC meeting, and more than 1,200 responses. The plan and research program focus on seven areas: the pathophysiology of CFS, the causes of CFS, diagnostics, in-hospital and pharmacologic studies, treatment and management of the illness, provider and public education, and CFS in children.

Dr. Miller said that CDC has made considerable progress in addressing the peer review panel's related concerns about lack of engagement with government public health agencies, lack of participation in large CDC databases, and lack of participation in the Epidemic Intelligence Service (EIS):

- CDC has recruited an EIS officer and is planning on recruiting the next class of EIS officers. A specialist epidemiologist will be associated with that program.
- The CFS program office has presented abstracts at meetings of the Behavioral Risk Factors Surveillance System, Agency for Toxic Substances and Disease Registry, and the Public Health Information Network.
- Program officials have met with the National Association of County and City Health Officials and the Association of State and Territorial Health Officials to discuss how to address their CFS constituents.
- The program is collaborating with NIH to evaluate a possible role of human herpes virus 6 (HHV-6) in CFS.
- The retrovirus laboratory is looking at the populations from the Wichita and Georgia studies and using split samples from the Whittemore Peterson Institute (WPI) to try to confirm those results.
- The program is looking at using molecular techniques to study a number of etiologies by partnering with people outside of CDC.
- The governor of Georgia contacted CDC requesting that that it determine the prevalence of unwellness in adolescent wards of the state. Using the foster care systems allows for early intervention with long-term follow-up.
- The program is collaborating with the Mayo Clinic on its epidemiology project to study the risk factors associated with the incidence of CFS in the population of an entire county.
- Some have requested moving the CFS program to a chronic disease center. There are various options being considered by the new CDC director.
- The 2009 CFS program has so far published 18 peer review papers, with three more in press and 14 more going through clearance.
- As of September 30, 2009, the public awareness campaign public service announcements have aired 16,000 times reaching 115 million viewer impressions in 129 hours of air time for a \$966,000 value.
- In the third quarter of 2009, 6,500 copies of the CFS patient brochure has either been directly distributed or downloaded from the websites.
- The CFS toolkit for professionals has either been distributed or downloaded almost 11,000 times.

Committee Discussion

In reference to WPI's announcement about the XMRV virus, CFSAC members expressed dismay over the comment of Dr. William Reeves, the CDC CFS program chief, to the *New York Times*: "If we validate it great. My expectation is that we will not." Dr. Miller replied that while he cannot address Dr. Reeves's comment, he can point out that Dr. Reeves is not going to be doing the laboratory work to validate the XMRV study. It will be done in CDC's retroviral laboratory.

Dr. Klimas expressed concern that the CDC is designing that study around the agency's Georgia study, which defined CFS as unwellness and used a group that was clearly not homogeneous. She contended that researchers stopped retroviral work in 1993 because the CDC slammed the door shut tight, declaring that enough had been done to demonstrate that it was no longer worth pursuing. The funding then dried up for retroviral work. She warned that if done poorly, the CDC study could do great damage to the field and asked the agency to consider the use of the well-defined cohorts of outside researchers. These cohorts, she said, were defined in research settings for comparison. Dr. Miller encouraged any researcher to contact the retrovirus laboratory and offer samples.

Dr. Hartz asked whether the CDC has the enormous resources that would be required to accomplish everything in the five year plan. Dr. Miller said that it is a strategic plan looking at the broader picture. The agency expects to address every part of the plan but given budget uncertainties, cannot predict the exact dates of when various components will be accomplished. He noted that emergencies such as H1N1 crop up and shift priorities.

Dr. Klimas asked whether the CDC has considered funding research on post-H1N1 onset of CDC. Dr. Miller said that the program is aware of the opportunity and that he would find out and report on any plans.

Presentation: XMRV Association with CFS

Dr. Daniel Peterson, Medical Director, *Whittemore Peterson Institute*

Please note: The following section highlights key points made during the presentation. Access to any presentation text and accompanying documents is available at: <http://www.hhs.gov/advcomcfs/meetings/presentations/091029.html>.

- Results are exciting but they are quite preliminary. I hope that my presentation injects a scientific stimulus package into the field of CFS research.
- It is important to differentiate XMRV from the other mouse viruses that are in the family of gamma retroviruses. A phylogenetic tree developed with gene sequencing demonstrated that the XMRV isolated from the CFS patients was

similar to but not identical to the XMRV from patients with prostate cancer. In addition, the XMRV from CFS patients is phylogenetically quite disparate from the mouse retroviruses, making it extremely unlikely that the CFS-related viruses resulted from mouse contamination in the lab.

- The XMRV discovery resulted from an unusual collaboration of the WPI, NCI, and the Cleveland Clinic. The collaboration demonstrates what can be accomplished in a relatively short time with relatively limited resources when organizations combine expertise that no one entity would have had on its own.
- The CFS study cohort reported in *Science* magazine was from the WPI repository.
- Research samples came from California, Florida, Nevada, New York, North Carolina, and Oregon. Repository inclusion criteria included a CFS diagnosis and an age range of 18-75 years. Study characteristics: 67 percent women, which reflects the gender incidence of CFS; a mean age of 55; and 320 control samples roughly matched by age, sex, and geographic distribution. The mean age is slightly older because samples were from researchers who had been following the populations for a long time.
- Critical questions: How is XMRV transmitted? Does the infected person mount an immune response and can we manipulate it for the patient's benefit? Does XMRV infection alter the risk of cancer development in CFS? Can we develop immune-based therapies for CFS?
- Clinical networking is critical with an agent like XMRV that can be studied across regional borders.
- Reliable CFS researchers have repeatedly reproduced certain findings: RNase L dysfunction in the antiviral pathway, low natural killer cell number and function, abnormalities of the innate immune systems with activated T cells, and production of inflammatory cytokines.
- XMRV is a simple virus that encodes only for structural proteins, so existing HIV-like therapies may not apply.
- XMRV is not ubiquitous and is not benign.
- Of particular concern: Approximately 4 percent of controls tested positive for XMRV.
- The research demonstrated the presence of the virus in both B and T cells of CFS patients.

- White blood cells from three patients were able to infect the prostate cell line. Controls were not able to do so.
- Researchers were able to transmit the infection with cell-free fluid. This means that there were active Virions in the plasma of these patients that could infect cell lines.
- In a significant proportion of patients, there was demonstrable envelope antibody present. 99 of 101 CFS patients had some evidence of activity of this retrovirus.
- Subsequent to the *Science* article, NCI and the Cleveland Clinic did studies with unrelated cohorts for independent evaluation outside of the WPI laboratory. Results: 60 percent tested positive for XMRV using polymerase chain reaction technology; about 87 percent tested positive using the co-culture technique and 53 percent of the plasma tested positive using the co-culture technique.

Other areas that WPI is investigating:

- Familial transmission of XMRV.
- XMRV associated with neuroimmune diseases such as multiple sclerosis, FM, autism, and Gulf War Illness.
- WPI patients with gamma T cell clonal rearrangements.
- Group of WPI patients that has developed lymphoma, leukemia, or related disorders.

Frightening finding: Researchers took plasma frozen from a patient in 1984, thawed it, and were able to infect cells with XMRV.

Hypothesis of XMRV disease progression is similar to that of HIV: acute infection, antibody response, and an ultimate failure of the immune system that may be NK cell dysfunction that results in significant, prolonged disease. This model could be easily tested and this should be done rapidly and judiciously.

Answering a question about the legal implications of spreading XMRV via blood transfusions, Dr. Peterson noted that he has already been approached by two attorneys eager to pursue the subject on behalf of their clients. The institute has cohorts of patients who became ill post-transfusion and one in particular where the blood donors have been located. WPI plans to test these donors. Dr. Peterson said that he is advising his CFS patients not to give blood.

Annette Whittemore, Founder and President, *Whittemore Peterson Institute*

Ms. Whittemore told CFSAC that her adult daughter has been ill with CFS for 20 years. CFS now has the attention of the government and the world because they have been given a piece of the CFS puzzle that cannot be ignored—XMRV. The virus:

1. Ends the debate over whether or not CFS is a psychological disorder.
2. Demands serious attention from government health agencies in the form of research funding and a response coordinated among NIH and outside researchers to complete the work as rapidly as possible. Patients deserve to know that they are infected and to be offered treatment. Funding should be equal to the amount provided to address other serious infectious diseases.

Perspectives on XMRV and Related Retroviruses

Dr. John Coffin, Principal Investigator, Tufts University

Please note: The following section highlights key points made during the presentation. Access to any presentation text and accompanying documents is available at: <http://www.hhs.gov/advcomcfs/meetings/presentations/091029.html>.

What is known about XMRV:

- Has been reported in 67 percent of CFS patients, but further study may well show that the frequency is closer to 100 percent representation.
- Can be cloned from prostate cancers unlike any other infectious virus appearing in published scientific literature.
- Has raised debate over whether the virus is in stromal cells or tumor cells.
- May be associated with Rnase cells but this remains to be worked out.
- The association with CFS is much clearer than with prostate cancer because researchers can get live virus out of peripheral blood mononuclear cells (PBMCs) and plasma.
- In activated PBMCs, it is present in an impressively high fraction of cells.
- The virus isolated is infectious for a number of human cell lines.
- Is present in 4 percent of control samples, although these are not unbiased samples in the case of prostate biopsies that were nonmalignant but were hyperplasia.
- There may be local bias because all samples were local. It is critical to get a handle on the actual prevalence in the United States and worldwide.
- There is already evidence for some worldwide association in an unpublished paper from Japan in which XMRV was found in blood samples from the Japanese Red Cross.
- A striking aspect of WPI findings is how close XMRV and xenotropic MLV are to each other. A patient who has been infected with HIV for two weeks has a greater diversity in the virus population. This implies that there are very few cycles of replication that separate the XMRV that is in one person from the virus that is in another. This suggests that the virus is not undergoing ongoing replication during the course of infection of a single individual. This is not good news for the use of antiviral therapy, but it is good news for development of a vaccine because genetic variation would not be a significant roadblock.

It is important to determine whether XMRV exists in mice, how XMRV got into humans, and how humans transmit XMRV.

What we do not know about XMRV:

1. Its role in CFS, prostate cancer, or other disease. There is one paper on XMRV's association with CFS and two on the virus's association with prostate cancer and they do not completely agree with each other. There is much that remains to be done. The first thing is to establish what role this virus has in CFS. Is it a cause, a passenger, or a coincidence?
2. The incidence and prevalence in the human population. In order to do these studies, it is important to have reliable assays. Immunological assays are difficult.
3. Distribution in the human population. Are there possible clusters of infection or is it generally widespread?
4. Mode of transmission. This is currently unknown.
5. Origin. The close relationship of these viruses means that it almost has to have come from mice. But is this happening today and is it happening all the time? Or did it happen once a long time ago, and the virus is now being transmitted at a low level in the human population?

Cautionary note – Unreliable tests for XMRV are already being sold on the Internet.

Committee Discussion

Dr. Hartz asked about a reasonable alternate explanation for the striking correlation between XMRV and CFS such as CFS patients being more susceptible to the virus. Dr. Coffin said that research results present strong evidence of cause and effect but the results are not conclusive.

Dr. Glaser said that as researchers continue their work on XMRV they must take into account what is known about other viruses such as HHV-6 and EBV. One or more of these viruses may also be required for CFS, or one virus may activate the latent form of another. Dr. Coffin said that the critical issue is finding the real trigger for CFS. Other viruses may be involved in the pathophysiology of the disease but not cause it. He recommended starting simply with uncovering the role of XMRV, then working up to the pathophysiological involvement of other agents. Dr. Glaser emphasized the importance of sharing reagents from lab to lab to make direct comparisons by using the same

serum plasma samples to do simultaneous studies on XMRV and other viruses such as EBV and HHV-6.

Dr. Oleske maintained that using the newborn maternal model to study perinatal transmission may be as important for the study of XMRV as it was in studying HIV. **Dr. Jason** raised the issue of XMRV activating other viruses and the need for strict laboratory standards to ensure the best science. Drs. Coffin and Peterson agreed, noting possibilities such as antibodies interacting and producing false positives, and other issues of cross reactivity.

Dr. Klimas asked whether a low level active infection without significant replication could still produce considerable viral product. Dr. Coffin said that such a scenario is possible even if the virus is not replicating. There could be a sufficient level of antigen to drive a T cell response.

Dr. Hartz asked Dr. Peterson if he has ruled out a single infectious agent for CFS. Dr. Peterson said that there have to be cofactors and they need to be determined.

Dr. Oleske reiterated the importance of collaboration as opposed to competition among laboratories. He pointed to the lessons learned during the early days of coping with HIV when massive delays were caused by multiple labs and clinical services doing assays in the same way with the same techniques. Dr. Coffin told Dr. Oleske that NCI called a meeting in June after the first rumors of the XMRV study. This meeting included as many interested parties as possible to discuss ensuring that researchers do not go down the same road as HIV.

Dr. Bateman raised the importance of carefully choosing and validating the type of patient chosen for a study such as the one done on XMRV. Dr. Peterson said that results are not meaningful to a clinician if he does not understand the characteristics of the patient population.

CFSAC members discussed how the Whittemore Peterson findings have legitimized CFS as a valid research area, including the recognition that more people may be infected with CFS than are infected with HIV.

Dr. Jason asked whether the NCI meeting discussed blood bank safety issues, whether the CDC was involved, and what Dr. Coffin's thoughts are on patient selection. Dr. Coffin agreed with Dr. Peterson about validating assets with a well-defined set of patients, adding that controls should be similarly well defined. He said that one representative from CDC—a scientist with research interests—attended the 25-person NCI meeting. Attendees did discuss blood supply safety and agreed that it needs to be addressed, but reached no conclusions.

Dr. Papernik noted that an association between XMRV and prostate cancer has been known since 2005 and there may be some information available from blood banks on prevalence of the virus. Dr. Coffin said that because there was no epidemic of prostate

cancer that would suggest that it is caused by an infectious disease, the findings did not set off as large a red flag as they probably should have. **Dr. Hanna** added that NHLBI was not concerned about blood safety related to prostate cancer based on the results of several studies with huge samples. The real issue for CFSAC is XMRV's relationship to CFS.

Several CFSAC members noted that a definitive blood test does not yet exist for the presence of XMRV. Dr. Klimas asked for a timeline for a commercial blood test. She expressed concern over CFS patients taking antiviral drugs before they have had such a test. Dr. Coffin said that a test could be available within six months but cautioned against anyone counting on this timeline.

Dr. Coffin said that as far as a treatment drugs are concerned, researchers first need to learn about the pathogenesis, then conduct controlled trials. He noted that researchers already know that some drugs are effective against XMRV in the lab.

Dr. Jason asked Dr. Coffin whether the resources are available to continue to analyze data and conduct CFS research and if not, what recommendations CFSAC could make to help make those resources available. Dr. Jason asked Dr. Peterson how he feels about collaborating with the CDC.

Dr. Coffin replied that the time frame is important in funding research. In the short term, resources are redirected from other ongoing work that does not have a similar immediacy or focus. Although this can be disruptive, many labs have the ability to devote a fraction their resources to CFS over the short term. He continued that NIH has pockets of money that it can tap to support one or two people in a lab. Over the long term, CFS research needs a specified funding mechanism such as an RFA, new money from Congress, and/or a more long-term reallocation of resources.

Dr. Peterson said that historically, there has been no collaboration with CDC. He said that given the magnitude of recent CFS research findings, the need for collaboration is an understatement. Continued research is a project that requires the resources of the CDC and NIH to take it many levels above what has already been done.

Ms. Artman expressed concern that some in the CFS community may give blood as an act of protest over lack of research funding. She underscored the message that any currently available blood test for XMRV cannot assure the safety of the blood supply and urged all CFS patients not to give blood. She concluded that no one should have to suffer with CFS.

[Dr. Jones called a 10 minute break in order to set up a telephone line for public testimony.]

Public Comments

The following section highlights key points made by witnesses who testified during the public comment session. Access to the complete text of witnesses' written testimony is available at: <http://www.hhs.gov/advcomcfs/meetings/presentations/091029.html>.

Marly Silverman

I want to speak today about the three R's: reconciliation, restore, and resolve.

Reconciliation is needed in our overall community. For far too long, the CFS/ME community has been embroiled in an unwanted and undesirable dissention with the CDC and other government agencies regarding the approach used for CFS/ME. This anger and frustration on both sides have obfuscated the real issues. Recent scientific discoveries about CFS are the lifeline that we have been waiting for a long time. We understand the potential ramifications if we don't embrace the possibilities. It is unfortunate that the government does not realize we are all in this together.

Restore the lack of trust of the patient advocacy community toward the CDC, NIH, DHHS, and our government. This lack of trust is fueled by the lack of transparency, action, and results. With the recent scientific findings of the XMRV virus and its correlation to CFS/ME and prostate cancer, the prime opportunity to repair past wrongs is here. We must all be open to the possibilities that this discovery is an exciting piece of information that needs to be aggressively investigated by the CDC and other members of the scientific community.

Resolve—We want to see a strong resolve from our government in getting the job done. It is time for a CFS program leadership change at the CDC so that one of the most prestigious health agencies in the world can do its job in a fashion that is truly state-of-the-art by 21st century standards. We are in the middle of a flu pandemic. Is the CDC keeping tabs on those who are getting very sick after a bout with the flu and whether they are progressing to CFS?

I am delivering to you a petition by CFS patient and advocate Tom Kindlon that has 1,893 signatures. His petition addresses the problems created by the current empirical CFS definition used by the CDC.

Robert Miller

I have been ill for more than 20 years.

I am glad that NIH is beginning to fund the Whittemore Peterson Institute because it is the CFS community's Center for Excellence. But there is an urgent need to expand this research of a new human retrovirus and to understand XMRV's function in CFS.

I have been here before asking you to fund \$100 million in CFS research. Now, based on the XMRV discovery, I don't believe that will be enough, but funding must still come now. I know that XMRV research will be funded for cancer, but I'm here to make sure

that our new Secretary of Health and the NIH fund XMRV research as it relates to CFS. Now is the time to fully fund the Whittemore Peterson Institute and other regional CFS centers. We should have centers of excellence equal to HIV and cancer centers.

While we need funding, I don't believe that any more should be wasted on the CDC until they have a leader who believes that CFS is urgent and real. I am appalled that the CDC allowed Dr. Reeves to comment publicly on the critical funding of XMRV without serious thought.

Courtney Alexander

This is a rare moment in the history of CFS. We have a scientific breakthrough in the discovery of the XMRV retrovirus and its prevalence in CFS. Every representative from our Federal health agencies sitting in this room needs to understand that the playing field has shifted. They found it, now you need to fund it. The Secretary of Health needs to provide \$100 million in immediate funding for:

- CFS centers of excellence as recommended by CFSAC.
- Additional research to answer the many critical questions raised by the XMRV finding.
- Clinical trials on treatments for CFS and XMRV.
- Development of diagnostic tests.

A substantial portion of the funding should be earmarked for the Whittemore Peterson Institute. While we desperately need such centers in lots of cities, we need to take advantage of what has been created in Reno to quickly get our arms around this devastating new human retrovirus and all its implications for CFS.

The CDC director should never have allowed Dr. Reeves to comment on such a profound event with reckless abandon of science and CFS patients. A change in CDC leadership has been endorsed by virtually everyone in the patient community and by CFSAC. It is past time that the Secretary acts on this recommendation also.

The only place that my husband [Robert Miller] can get Ampligen is in Reno, NV. The only medicine that stabilizes his immune system is only available in Reno. That is a crime. After 10 years of clinical trials, the FDA is still stonewalling and we can't wait any longer. To the FDA representative assigned to CFSAC, I ask you: have you ever had to move your family to get a medicine that has 20 years of safety data, but no approval?

[Ms. Alexander also delivered a statement from Anita Patton, a CFS patient who lives in Reno, NV.]

Dharam Ablashi

I am the scientific director of the HHV-6 Foundation, which supports research on the role of virus in chronic diseases including CFS. I co-discovered HHV-6 in 1986 while at the National Cancer Institute (NCI).

I am sorry to say that over the years, several people in leadership positions both at NIH and CDC have made it clear that they do not believe that studying infectious agents in CFS is important. Much provocative work on infectious agents and CFS has languished for lack of funding. The CDC has made several assumptions that we believe will prove to be in error:

1. If a pathogen exists it can be found in blood serum.
2. If there is a pathogen, it is only one pathogen, not eight to twelve pathogens that cause variations of the same syndrome.
3. The timing of sample collection is unimportant.

Patient samples from newly diagnosed CFS cases offer the best chance of finding evidence of an infectious agency. Studies should be organized to examine samples from these patients separately from those who have been ill for decades.

Most of the studies done by the CDC have been on serum. However, many pathogens cannot be found in the serum because they do not circulate in the peripheral blood after the initial infection. We propose that CDC invest the majority of its research budget in exploring pathogens in CFS with particular emphasis on examining spinal fluid, brain tissue, cardiac tissues, and gut biopsies.

Joan Grobstein

I've been a physician since 1977; I've had ME/CFS since 1999. I suggest the following recommendations to Secretary Sebelius:

1. No taxpayer dollars should be wasted on ME/CFS research that uses the Reeves definition. All federally-funded research should use the Fukuda criteria and the Canadian Consensus definition.
2. Abandon the CDC's current proposed five year plan. Ensure that CFSAC's previous recommendation for a change in the CFS leadership at the CDC actually happens. The new leadership should propose a new five year plan which should then be reviewed by an *unbiased* panel. Meanwhile, make the taxpayer-funded data that the CDC has already collected available to all researchers to analyze.
3. If the XMRV connection to ME/CFS is confirmed, initiate a Congressional inquiry into why Elaine DeFreitas' research into retroviruses and ME/CFS was not pursued in the early 1990's.
4. Increase funding for ME/CFS research. Designated funding for a collaborative trials network is imperative.

Janice Bell

I am delighted to see that CFSAC is taking new research findings seriously.

I came down with CFS on May 2, 1987. In addition to the onset of classic symptoms such as sore throat, fever, and muscle weakness, I developed paraphasia. Although I had scored a 760 on my math SAT, I found myself unable to do simple arithmetic. Despite being a Fulbright Scholar with a doctorate in art history, I lost visual recognition skills for objects such as forks and bowls. For a long time I struggled with depression at the tremendous losses I'd suffered.

But I know that I am one of the lucky ones. I had the research skills, brain power, and resources to study human physiology and holistic treatments from California to the Caribbean. I am asking CFSAC to give more attention to nutritional interventions because pharmaceutical companies do not have the incentive to undertake this kind of research. Here is a brief list of such interventions:

- Vitamin B-12.
- Specific antioxidant supplements designed to scavenge peroxynitrate.
- Methylation and reduced glutathione.
- Amino acid therapies, particularly intravenous administration of amino acids.
- Dr. Sarah Myhill's protocol for reversing mitochondrial dysfunction and Dr. Kenneth De Meirleir's discovery of increased H₂S in ME/CFS patients.

To control costs, we need to stop turning natural nutritional products into drugs just because a pharmaceutical company wants to market it. This has happened in the past year to BH₄ (tetrahydrobiopterin) and a natural, active form of Vitamin B.

In addition, I ask the government to look into:

- Peptides that disable viral penetration into the cell such as the one discovered by Dr. Candace Pert of Georgetown University.
- Peptides reported by the Thai company Immunitor to extend the life span of individuals with late-stage AIDS.
- Transfer factors and other markers of healthy immune function that could explain why 3.7 percent of the healthy population is able to harbor XMRV without becoming symptomatic.
- A new case definition for CFS. The Canadian definition of ME is a more accurate description of the symptoms.
- In the event that XMRV does not turn out to be the marker sought, functional markers including organic acids, amino acids, and methylation markers in order to diagnose new cases before irreparable oxidative damage occurs from overexertion.

Ruth Bell

It's extremely painful to have a child [Janis Bell] who has been sick for many, many years. It has been most painful when physicians have told her, "it is all in your head," or "we don't know what to do to help." It is most painful that, when she sometimes feels a bit better and we all have hope that she is improving, she relapses back to weakness and exhaustion and we go back to feeling dismayed and hopeless.

Let me describe the differences I see in my daughter so that you can get a sense of the devastating impact of CFS:

She and her young daughter lived in a university town where Janis was an associate professor. I was aware as she was fighting a custody battle, being a single parent, and working full time, that she was feeling more and more exhausted. It was extremely painful that after winning the custody battle in court, she has to relinquish custody of her child to her former husband because she was too ill to take care of her child.

She began studying the syndrome on her own. This led to her study and subsequent certification as a doctor of naturopathy.

I am thankful that her partner is a generous and extremely helpful man, quick to take care of many of the chores. She could not have made it on her own as there were days when she could not stand for more than a few minutes let alone go to the grocery store.

I am grateful that I am able to help but other parents may not be in such a position. It is unfair and sad that I can run rings around my daughter energy wise although there is more than a generation between us and I have a bad back.

Carol Geraci (via phone)

The United States is facing a serious health crisis that millions of Americans have contracted a disabling AIS-like illness. The U.S. is in great risk as this epidemic continues to take the lives of millions. Countries like Japan, Germany, and many others are taking this disease very seriously. Our press has been unkind to CFS because they follow the lead from the CDC.

Although I may not be alive in two years to get treatments, as I came very close to death this year, I will spend every waking moment I can trying to get Congress to conduct hearing on the travesty of how this illness has been marginalized by the CDC.

My best years are gone—my 20's and 30's—and I cannot get them back. I had a wonderful life ahead of me. I wanted children and a family; I once had a wonderful career that was cut short because I got EBV/mono and I was told I had the yuppie flu. I owned my own computer consulting business only to lose everything because I could no longer work.

I present the following agenda of action items:

- Have a meeting with the best ME/CFS doctors around the country and at the Whittemore Peterson Institute to see what tests and treatments they give. Whatever these doctors are using to treat patients should be made known to other doctors immediately starting with those who already treat CFS.
- Make immunoglobulin available for those with subclass IgG deficiency as well as for those who are deathly ill, become too weak, or have the treatment recommended for them by their physicians.
- Begin clinical trials immediately.
- Improve public awareness about ME/CFS and change the name CFS to include ME or neuro-immune disease. The CDC must inform hospitals, doctors, colleges, and the media how severely ill people with CFS are.
- Reach out to the pharmaceutical companies, as I am sure that if they know there are 1-4 million who suffer from this disease, they will sponsor clinical trials for drugs such as Artunsunate used in Norway and Zadaxin used in Italy.
- Give up the notion [at the CDC] that ME/CFS patients are mentally ill.
- Stop all studies not relevant to treatment.
- Update the CDC website to include information that ME/CFS is a real disease, not a syndrome.

[Dr. Oleske called a break for Subcommittee Lunch.]

Committee Discussion

CFSAC Recommendations

Dr. Hartz expressed frustration over not knowing what is expected from CFSAC; especially not knowing which recommendations were useful, which were not, and if they were not, why they were not. He said that CFSAC does not get enough guidance on making effective recommendations.

Dr. Jones said that she recently completed an annual report on the committee's activities and costs, which included evaluating the status of CFSAC recommendations. Out of 38 recommendations, she found distinct progress on about nine, and expected progress on seven. She noted that not enough time has elapsed to show movement on May 2009 recommendations.

Recommendations showing most progress were:

- Focused on specific issues that DHHS could implement as an organization.
- Presented opportunities that leveraged momentum on activities already underway at *ex officio* agencies to which CFSAC could give extra impetus.

Recommendations showing the least progress were the most micro agency level. CFSAC advises the DHHS Secretary and while that person oversees all agencies, he or she delegates tremendous discretion to agency heads. Dr. Jones noted that CFSAC's record of getting almost half its recommendations acted upon is "quite good" for a

DHHS advisory committee. She said the new CFSAC charter to be drawn up in the fall of 2010 will be an opportunity to fine tune how the committee conducts its work.

Dr. Hartz called for more specifics on exactly how recommendations were acted on and why. CFSAC should fully understand the guiding principles for making more effective recommendations.

Research Subcommittee Report

- **Dr. Glaser** suggested that CFSAC schedule two research-related speakers at each meeting to join practical discussions about ongoing CFS research and how it translates into applicable results for patients. **Dr. Jason** suggested that a discussion of case definitions would be a good topic.
- Dr. Glaser provided data on the degree of expertise on the CFS Special Emphasis Panel (SEP) at NIH's Center for Scientific Review (CSR). On three previous SEPs, only 15 percent of reviewers conducted research that had anything to do with CFS, and no reviewers had an expertise in etiology or biomarkers. Two of the most important aspects of CFS research are finding etiological agents and biomarkers for diagnosis.

CSR Director Cheryl Kitt has acted on CFSAC's recommendations, said Dr. Glaser. Out of the 17 members of the October 2009 SEP, 41 percent have at least some background in CFS and an additional 18 percent have a "questionable" background in the disease. However, no members are studying biomarkers, retroviruses, EBV, or HHV-6. Dr. Glaser said that researchers are not going to write grant applications if the investigators do not think that their proposals will win approval.

- Dr. Glaser supported a recommendation that the CFSAC chair meet twice a year with the DHHS Assistant Secretary to update him or her on CFS issues and to transmit his or her feedback to the committee.
- **Dr. Jason** said that a mechanism is needed to coordinate the sharing of specimens and findings among researchers and various DHHS agencies.
- Dr. Jason said that after reviewing the CDC's five year CFS research plan, subcommittee members wondered how the agency will pay for the plan proposals in addition to funding ongoing activities. The subcommittee is concerned that the plan does not prioritize activities.
- Dr. Jason said that the subcommittee wants to find out what happened to CFSAC's May 2009 recommendations.

[Dr. Willis-Fillinger arrived at the meeting.]

Dr. Oleske supported Dr. Hartz's recommendation that the CFSAC chair and Designated Federal Officer meet regularly with the DHHS Secretary or the Secretary's representative. Dr. Oleske emphasized centers of excellence and collaboration among clinical trial groups as key to finding answers for CFS diagnosis and treatment.

Ms. Artman said that research is overshadowing treatment in CFSAC discussions. She said that patients are desperate for doctors who will treat them and that CFSAC must also discuss how to bring clinicians into the field. She noted that boutique clinics and high-end treatment facilities exist, but many CFS patients cannot afford them. There is a huge care gap, she said, and family care practitioners do not have time to treat CFS patients. Dr. Glaser emphasized that CFSAC must carry that message to the DHHS Secretary. Dr. Oleske said that anyone advertising themselves as a primary care practitioner should know how to treat CFS.

Education Subcommittee Report

Ms. Healy described the CDC education effort as a good start but said that it has not provided what many primary care physicians need to make them comfortable with treating CFS patients. She pointed to AHECs as a valuable education opportunity and called upon CFSAC *ex officio* members to consider for the next meeting similar opportunities that may exist in other agencies for provider and patient education. She added that opportunities may exist in other Federal departments, citing the Veterans Administration's (VA) disease management guidelines.

Noting the need for more intensive continuing medical education (CME) opportunities, Ms. Healy reiterated that clinical centers of excellence would provide on-the-ground, in-depth training to medical practitioners and named HRSA as a possible funding source. Citing the recent CDC webinar on H1N1, she wondered whether the agency could produce similar web-based CFS education.

Dr. Klimas commented that moving from diagnosing CFS to treating the disease is the next step in CME. Possible venues include:

- Certification programs organized in CFS clinics already in operation.
- Seminars at the meetings of primary care conferences. She said that when such lectures are given, they attract high attendance, demonstrating the "burning desire" of primary care physicians to know how to treat CFS.
- A DHHS-sponsored workshop of experts to develop treatment guidelines.

Dr. Klimas acknowledged that centers of excellence would be the ideal venue for such CME, but added that doctors are needed right now to treat CFS and the field cannot wait for centers to begin needed training.

Ms. Healy wondered whether in light of recent research discoveries, the timing may now be right to begin setting up a state of the science meeting that would culminate in a letter from the Surgeon General (SG). **Dr. Hanna** noted that NIH will hold a state of the

science conference in 2011 and that current and former CFSAC members could provide input. Dr. Jones said that she will confirm that past committee members can be consulted as expert resources.

Dr. Klimas inquired whether a working group of experts could gather the day before the CFSAC meeting to begin drafting CFS clinical treatment guidelines. Dr. Jones said that she would investigate that possibility.

Dr. Jason commented that with many CFSAC members' terms ending on January 3, 2010, the timing may be right to consider the committee and subcommittee structure, the panel's most important goals, and whether the current structure is the most effective way to support those goals.

Patient Care/Quality of Life Subcommittee Report

Ms. Artman discussed the subcommittee's letter to SSA asking for data on how it handles CFS disability claims compared to other chronic conditions. She said that the data will be ready for the next CFSAC meeting and that a substantial amount of time should be devoted to examining the SSA statistics. She said the subcommittee has devoted time and energy to developing questions that will produce informative answers that encompass many aspects of CFS, including pediatric cases. She said that the subcommittee was stonewalled when it attempted to collect data from medical providers and insurance companies and that the information from SSA will be as important as recent research discoveries in determining how CFS is perceived as a disability. She concluded that as long as CFS patients are denied access to care, it does not matter what research is being conducted.

Mr. Newfield expressed gratitude to Ms. Artman for inspiring and leading the subcommittee and providing the perspective of the patient population. He also emphasized the frustrations of accessing information from insurance companies.

Mr. O'Connor confirmed that initial disability claims and reconsiderations are both generally evaluated in the state in which an applicant resides. Adjudication hearings are done at the nearest location. Some hearings are conducted via videoconferencing when patients reside in remote locations.

Mr. Newfield noted that it is easier to get a CFS disability claim approved by SSA than by a private insurance company, although it takes longer. Claims are more successful when adjudicators can see patients and "put a face to the illness."

Dr. Snell commented that effective, cooperative *ex officio* members are invaluable when CFSAC is seeking information.

CFS and FII/MBP

Dr. David S. Bell, Associate Professor of Pediatrics, State University of

New York at Buffalo

Please note: The following section highlights key points made during the presentation. Access to any presentation text and accompanying documents is available at: <http://www.hhs.gov/advcomcfs/meetings/presentations/091029.html>.

Dr. Bell presented a 1986 case of pediatric CFS:

- A 16 year old girl, although bedridden for six months, could not obtain a specific diagnosis from her doctor and was referred to Social Services because of school truancy.
- She was considered a child abuse victim because her parents did not force her to attend school.
- Failure to attend school was considered educational neglect (a form of child abuse) on the part of the parents. Court action was begun to remove the child from her family.
- The school refused educational support at home because the child had no medical diagnosis.
- Although a psychosocial evaluation revealed a healthy, intact family; the student had no history of drug abuse; and the family had no history of neglect or abuse; legal proceedings continued for one year and the parents spent \$20,000 in legal fees to maintain custody of their child.
- Social Services dropped the case after two years.

The issue is the diagnosis of CFS. While there have been variations on specific diagnostic criteria, they are fairly simple—extraordinary activity limitation and a number of symptoms in various symptom categories.

The issue that comes up from a legal and child abuse perspective is the broad category of somatoform disorders. Dr. Bell provided a list of these disorders, noting that factitious disorder is the one most commonly cited. In both factitious disorder and malingering, the interest of the patient is not to be treated, but to “enjoy” the status of being a patient or to obtain a medical diagnosis for personal gain. Dr. Bell commented on how extraordinary it would be for an adolescent to “enjoy” being bedridden for six months.

Munchausen’s by Proxy – In the past, this was the most common diagnosis given to pediatric CFS patients in cases such as the one described by Dr. Bell. Munchausen’s is defined as an illness in a child stimulated or produced by a parent or someone acting *in loco parentis*. Because the child’s acute symptoms abate when separated from the perpetrator, the diagnosis is usually made in a hospital by videotape. Dr. Bell concluded that a diagnosis of Munchausen’s is impossible in the case of a CFS patient.

Pediatric Condition Falsification (PCF) – Currently the more common diagnosis in cases such as the one above, PCF is defined as the intentional falsification of

symptoms by the perpetrator. The child victim is diagnosed with PCF and the parent receives a psychiatric diagnosis of Factitious Disorder by Proxy (FDP).

Hypochondriasis by Proxy – Maternal anxiety leads to an exaggerated perception of the child as sick. CFS parents are often described as over-involved because they do most of the talking during an examination. In fact, they are acting as the spokesperson for a sick child who has often already been seen by multiple physicians. FDP can be ruled out in a child when repeated presentations for medical care result from an illness that is wholly and credibly accounted for in another way.

CFS has been recognized by 1,500 papers in medical literature, according to Dr. Bell. It is not a questionable diagnosis. The physicians in the case above should have been able to diagnose CFS as a medical illness.

Dr. Bell presented a similar pediatric CFS case from 2009 in which the family spent \$120,000 to maintain custody of their child. Dr. Bell told CFSAC that he has been involved in 20 similar cases over the past 25 years with little change in the circumstances—CFS has diagnostic criteria but nobody pays attention to them.

Summary

1. CFS is a diagnosis that would specifically exclude PCF.
2. This information has not been distributed to pediatricians, child abuse agencies, and educators.
3. Medical abuse continues.

Dr. Bell recalled that five years ago when he was CFSAC chair, he sent a letter to the president of the American Academy of Pediatrics and received no reply.

Action Points

1. CDC and HRSA should draft a document stating that CFS is a serious illness that is not caused by child abuse or neglect.
2. CDC and HRSA should notify public and private educational facilities concerning the existence, prevalence, and symptoms of CFS. Schools have become good at diagnosing and managing learning disabilities and could do the same with CFS.
3. CDC and HRSA should insist upon educational support for an ill adolescent regardless of the severity. If a child is so ill that he or she cannot attend school, there is a good chance that the illness will persist and that child needs a good education so that he or she has more options to support him or herself.
4. A clinical diagnosis of CFS is needed that excludes PCF (FDP) unless proof of abuse is also found. CFS and abuse can be co-existing conditions.
5. CDC should educate physicians concerning the differences between CFS and PCF.

6. The American Academy of Pediatrics should contribute to diagnostic criteria and formulation of policies.

There have been a number of children in this situation who do not recover from CFS but nevertheless go on to lead productive lives. Some patients, however, have been so mishandled and hurt by the medical establishment that they become embittered and never recover. That is unnecessary.

Committee Discussion

Dr. Hartz asked how long it takes for Dr. Bell to sort out legal cases involving the misdiagnosis of CFS as abuse. Dr. Bell replied that the longest case has taken 10 years. The original court order forbade the parents from taking their child to any more physicians. Dr. Bell's first step is to conduct a family assessment to determine the probability of abuse, then assess the child's symptoms. Such a process should take half an hour, but on average, it often takes a year in the public system due to the bias against the illness and lack of understanding about a proper diagnosis.

Dr. Jason asked whether two factors contribute to the stigma associated with CFS—the name “chronic fatigue syndrome” and the CDC's contention that early childhood trauma is implicated in the majority of people with the disease. Dr. Bell replied that trivialization of the illness is still an enormous problem and that he is unhappy with the CDC's definition. He said that the clinical diagnostic criteria must emphasize the activity limitation and the cognitive and post exertional malaise symptoms. He expressed hope that biological markers will emerge in the near future.

Dr. Bell continued that recall bias is difficult to fight in an illness that cannot be explained. His CFS patients come from the same spectrum of good, medium, and troubled families as do children without CFS. Dr. Klimas noted that in her study of people affected by Hurricane Andrew, post traumatic stress disorder in CFS patients was most often caused by being disbelieved and trivialized for their disease.

Dr. Bell concluded that his past experience, including a CFS-like outbreak in Lyndonville, NY, leads him to urge that future research focus not only on XMRV, but on multiple triggers and co-infecting factors. He is currently conducting a study of the 60 children who fell ill in Lyndonville to find out what their symptoms are 25 years later.

Public Comments

The following section highlights key points made by witnesses who testified during the public comment session. Access to the complete text of witnesses' written testimony is available at: <http://www.hhs.gov/advcomcfs/meetings/presentations/091029.html>.

Kim McCleary

As President and CEO of the CFIDS Association, I believe I hold the unique distinction of having attended every single meeting of CFSAC and its predecessors since they were opened to the public in 1993. This morning's session was the best session of this committee, in my memory.

What has stumped this panel of CFS experts and all of us who have taken part as advocates over the years is how to mobilize our Federal resources to accomplish more research, medical care, and education—especially of doctors. There is now scientific momentum to fuel mobilization:

- NIH has participated in the XMRV research through the NCI's intramural program and NIAID's recent grant to the Whittemore Peterson Institute to support expanded research on XMRV.
- The ORWH has collaborated with the CFIDS Association to host a meeting of funded investigators last month at Cold Spring Harbor Laboratory's Banbury Center, with the outcome of unparalleled consensus that a formal research network linking CFS investigators would propel the field forward. We are moving forward to implement recommendations arising from the Banbury conference to create this network.

In spite of this progress, NIH CFS funding is at the same level as it was in 1993.

- *We urge CFSAC to recommend that NIH immediately issue an RFA* to capitalize on increased interest in CFS research arising from the XMRV publication and the promise of a formal research network.
- Six months ago, the CDC presented a draft five-year strategic plan. Its repetitive emphasis on psychosocial features, risk-conferring behaviors, and chronic unwellness reflects a disregard for and/or dismissal of the major criticisms of the draft plan loudly and plainly echoed by organizations and individuals at public meetings held in April and May and in written correspondence. *We implore CFSAC to aggressively challenge this plan* to protect the hard-earned progress of the past 16 years and not waste \$25 million that should fuel important research.

Sarah Turner

I have been sick for three years. My illness started with what I thought was the flu. I now work three days a week. Sometimes even that's too much.

- The most difficult part about living with CFS is that it's so unpredictable. I don't know when my symptoms will flare up and when they will subside.
- The other big challenge has been negotiating with my doctors and insurance companies. My doctor is sympathetic and she believes that my illness is real. But she knows of no treatment beyond rest and gentle exercise. She's not

curious about diet or alternative healing methods. So I've had to do my own research and try things myself.

- Until recently, I would have had nothing bad to say about my disability insurance. The system worked well for me and the benefits helped pay the bills. However, my claim was suddenly closed at the end of August and I'm now in the process of filing an appeal. They say my doctor has provided no medical evidence that supports my not being able to work full time.

What I'm asking from you:

- Please make research leading to objective diagnosis and treatment of CFS your highest priority.
- Please do all that you can to fix the way private disability companies deal with CFS in their policies and handling of claims.
- Please continue to educate doctors so patients won't be blamed for their illness when they try to get help.

Staci Stevens

Despite CFSAC's good work, there has not been a written response from DHHS to a recommendation since 2003. This is unacceptable and must be changed.

CFS is a physical disease and we can identify, characterize, and measure its most distinctive and disabling features. That is what we do at the Pacific Fatigue Laboratory, University of the Pacific [where I am founding Executive Director].

By contrast, the CDC recommends the use of self-report questionnaires to diagnose and quantify this illness. Questionnaires simply do not provide the evidence required by the Social Security Administration or long term disability carriers to diagnose medical illness or to determine a disability claim.

Statement read on behalf of psychiatrist Eleanor Stein, the IACFS Ambassador from Canada:

I would like to express my strong concern about the harm being done by using the 2005 empiric definition of CFS. This definition recommends diagnosing CFS using three self-report questionnaires: two of the three are nonspecific and erroneously include people with a wide variety of disorders including primary psychiatric problems. I cannot use the empiric definition in good faith in my practice; I rely on the Fukuda and the Canadian consensus definitions. It is my hope that CFSAC will make a public statement that the empiric criteria should not be used for either clinical care or research and that until a better definition is created the Fukuda and/or Canadian consensus definitions should be used.

Fred Friedberg

Six months ago the three major CFS scientific advocacy groups—the IACFS/ME [of which I am President], the CFIDS Association, and CFSAC—recommended new, open-minded leadership at the CDC's CFS research program. Despite this unprecedented consensus, the CDC has shown no indication of changing its CFS program leadership.

This is surprising given the agency's track record. After 25 years and more than \$100 million, CFS remains a stigmatized illness without substantive progress on public health policy or objective diagnosis and treatment. And the agency's five year, \$25 million plan fails to inspire any confidence that change will occur. In fact, the consensus recommendation of these scientific advocacy groups was based in dissatisfaction with the CDC ill-conceived and impossibly far-reaching five year research plan.

Quote read on behalf of Gundun Lange, member of 2008 external review panel that evaluated the CFS research program at CDC:

I am very disappointed that the CDC has not implemented important suggestions made by peer reviewers including establishing closer relationships with other traditional public health agencies to further promote CFS as a significant health concern. It is rather surprising that CDC has not shown any initiative to address obvious research questions posed by the H1N1 epidemic. Why are we not surveilling the population for post-infectious fatigue following H1N1?

Quote read on behalf of British scientist and geneticist Jonathan Kerr:

Research output on CFS from the CDC in the last five years has been principally in the areas of gene expression and mutation. These studies used patients who did not attend CFS clinics and were not diagnosed by recognized CFS clinicians. The findings of these papers do not lead anywhere and were not followed up by CDC. They do not provide insights into pathogenesis, nor do they indicate candidate treatment targets.

IACFS/ME recommends

- A continuing critical CFSAC focus on the CDC CFS program until the leadership is changed.
- A new scientific forum at CFSAC that allows biomedical scientists who wish to speak at the meeting the opportunity to do so.
- Permission for non-U.S. biomedical experts in CFS to participate in these scientific forums.

Cort Johnson

Mr. Johnson read a statement by Dr. Charles Lapp of the Hunter Hopkins Center in North Carolina. Dr. Lapp is a former CFSAC member:

- My patients complain that their illness is not accepted by the public, their families and their providers. Their doctors are unable or unwilling to treat CFS.

- Fellow practitioners are frustrated by a disease without a diagnostic marker that is believed to be psychiatric in nature.
- The CDC toolkit guidelines are simplistic, non-specific, and outdated. Only 1,700 providers have requested printed copies.
- In contrast, Dr. Lucinda Bateman and I wrote a web-based tutorial with the CFIDS Association that was promoted on Medscape. This program provided certification to 28,000 practitioners in the first six months. The Medscape course was straightforward and provided simple tools for diagnosis.
- At the 2009 IACFS meeting, six potential new CFS markers were suggested, none of which is being explored by the CDC because it is busy with epidemiological and sociological studies that have little potential benefit for CFS patients.
- The CDC leadership's research goals are old-fashioned, outdated, and unproductive. I support a change in CDC leadership that will support finding a marker for the illness, treatment guidelines, and education for practitioners and the public.

Marilou Regan

- My daughter Beth fell ill when she was 12 years old. Multiple doctors could not diagnose the illness. When she received a diagnosis at Children's Hospital of Philadelphia, she was told that nothing could be done for her and that she would have to live with her symptoms for the rest of her life.
- She was home-schooled for junior high and went through high school with no social life or friends.
- Due to her illness, she enrolled in a college close to home. She had to accept a failing grade due to illness, could not get class-attendance concessions from professors, and was told to consult a psychiatrist.
- She was denied Social Security Disability benefits and will lose health insurance coverage when she graduates.
- More research funding is needed and CFS needs to be recognized as a "real" disease that merits disability and healthcare coverage.

Nancy McGrory Richardson

- I am the education and outreach director for Hemispherx Biopharma, Inc.
- Hemispherx is sharing with Dr. Peterson its data set of samples collected from CFS patients.
- The company has submitted a preliminary design to the CDC for a longitudinal gene expression study in CFS patients. Outside researchers will be able to comment on the study design and participate in the study itself. One of the recommended end points is XMRV gag sequences.
- Hemispherx surveyed 11,000 rheumatologists at their 2009 scientific meeting:
 - 83 percent regularly see CFS patients.

- About half of these CFS patients were referred by primary care physicians.
 - Half of the CFS patients were diagnosed by a primary care physician, half by a rheumatologist.
 - Half of the rheumatologists who treat CFS patients were aware of the CDC's public awareness campaign and free educational materials.
- Among rheumatologists who treat CFS patients:
 - 20 percent said CFS patients comprise less than 10 percent of the patient population.
 - 65 percent said CFS patients comprise 10-30 percent of the patient population.
 - 15 percent said CFS patients comprise 30-50 percent of the patient population.

Janet Smith

- I am an urologist from Sioux Falls, SD. I treat interstitial cystitis (IC) which is controversial like CFS and also associated with the disease.
- A surprising number of IC patients, including teenagers, have undiagnosed CFS. They are reluctant to answer questions about CFS symptoms because nobody else has believed them.
- Both I and the patients have been called crazy when I refer them to another physician with the diagnosis of CFS.
- Insurance coverage is a problem.
- Very few physicians want to stick their necks out and diagnose CFS because there is no test or treatment.
- Physicians are not "getting it" despite the CDC's educational materials. It is a rare medical student who has heard of the disease.
- Regional centers of excellence like the Whittemore Peterson Institute could accurately evaluate and diagnose patients and return them to their local physicians with treatment plans. Local physicians could get colleague support through hotlines.
- I became acutely ill in 1994 and was diagnosed with pneumonia. I had to travel to the West Coast to be diagnosed with CFS in 1998. I am on Ampligen and have logged 3.5 million miles flying back and forth for treatment. I am alive and working full time due to the aggressive treatment of my CFS.
- CFIDS deserves as much attention and urgency as H1N1.
- My hope for the future is that medical textbooks will have a whole section on CFS with etiology, diagnosis, and treatments and that all physicians will know what CFS is.

Dr. Oleske thanked those from the community who attended the meeting and those who spoke. He said that the distinguished group demonstrates that people with CFS can still undertake occupations and duties.

Adjournment

Friday, October 30, 2009

Call to Order/Opening Remarks

Dr. James Oleske

Dr. Oleske called the meeting to order, pledging to ensure that any CFSAC recommendations approved at day's end would be delivered to and read by the HHS Secretary or her representative.

Roll Call, Housekeeping

Dr. Wanda Jones

Dr. Jones conducted roll call, determining that a quorum of 10 out of 12 voting members was present, with Drs. Glaser and Hartz absent. Alternate *ex officio* member Mike O'Connor represented the Social Security Administration (SSA).

Dr. Jones then informed meeting attendees of several logistical matters:

- Cell phones should be placed on the vibrate, mute, or off position.
- Members of the public must be escorted throughout the building, including when using restrooms.
- CFSAC staff is committed to the continuing accessibility of web casts of future meetings. A preliminary count of the previous day's webcast views totaled about 400. Views from the May 2009 CFSAC meeting—the first ever to be webcast—totaled about 107 on day one and about 70 on day two. Dr. Jones remarked that the increase in views confirms the value of the webcast.
- Audience members had access to water and a private rest area at the back of the meeting room.
- Public comments and a podcast of the meeting were to be posted on the CFSAC website as soon as they met accessibility requirements.
- Members of the public were reminded to provide their comments in writing for the record.

HRSA Update

Dr. Deborah Willis-Fillinger, Senior Medical Advisor, Office of the Administrator, Center for Quality

Please note: The following section highlights key points made during the presentation. Access to any presentation text and accompanying documents is available at: <http://www.hhs.gov/advcomcfs/meetings/presentations/091029.html>.

HRSA is the primary Federal agency for ensuring and improving access to healthcare services for the uninsured, isolated, or medically vulnerable. HRSA concentrates on improving access through the workforce, making facilities for healthcare services available in communities, and encouraging quality of care.

- HRSA provides clinical care for more than 20 million people—more than Kaiser (8.7 million) and the Veterans Administration (VA) (5.8 million) combined.
- One out of every 18 people living in the United States relies on a HRSA-funded clinic for primary care, including one in three people with incomes below the Federal poverty level.
- More than 8,400 physicians and more than 5,100 nurse practitioners, physician assistants, and certified nurse midwives work in the Community Health Center Program alone.
- HRSA emphasizes a multi-disciplinary clinical workforce designed to treat the whole patient through culturally competent, accessible, and integrated care. There is a major emphasis on team management as well as patient-centered care.
- Many health centers also provide educational opportunities for the next generation of clinicians.
- Health centers can be located by accessing www.HRSA.gov and clicking on “Healthcare Regardless of Your Ability to Pay”.

HRSA Supports Health Professions Training:

- Supports scholarships and loan repayments to clinicians in return for service in needy areas.
- Targets support for rural healthcare delivery and rural community health challenges.
- Emphasizes quality and measures performance.
- Emphasizes and provides training for culturally competent communication.
- Promotes adoption of health information technology.

HRSA and the American Recovery and Reinvestment Act (ARRA):

ARRA provided HRSA with \$2.5 billion, \$2 billion of which was targeted to expanding care at health centers. Within a few months of the legislation HRSA earmarked:

- \$155 million to establish 126 new health centers.
- \$338 million to extend hours, expand current services, and add staff.
- \$850 million to improve and expand physical sites, buy needed equipment, and pay for and implement healthcare information technology.

Within six months of ARRA's enactment, an additional 750,000 people in 39 states and two territories have benefited from increased access to healthcare.

ARRA has funded expansion of the National Health Service Corps (NHSC). NHSC is a 39 year old program that provides recruitment incentives in the form of scholarships and loan repayment. HRSA has supported 30,000 health professionals committed to service to the underserved. ARRA provided an additional \$300 million to add another 4,100 physicians, dentists, nurses, nurse practitioners, and other health professionals, effectively doubling the number of healthcare clinicians currently in the field.

ARRA provided an additional \$200 million to help rebuild the health professions training programs—with an emphasis on nursing—to build institutional capacity and support qualified students at colleges and universities.

HRSA Demonstration Programs and Collaborative Learning Projects

These programs and projects include teams of clinicians from across the country and are designed to create and test best practices to address health disparities and learn what works in the communities served. There is a strong emphasis on care that follows clinical guidelines and clinicians track outcomes with performance measures. Examples of collaboratives supported by HRSA include:

- Patient Safety Pharmacy Collaborative – working in 65 communities to test and develop quality ways to reduce handoff errors and ensure that patients receive the proper prescriptions.
- HIV/AIDS Learning Collaborative
- Organ Transplant Collaborative - working to increase the number of people who have access to organ transplants.
- Health Disparities Collaboratives - addressing diabetes, cardiovascular disease, perinatal, cancer, asthma, and depression.
- Federal Tobacco Collaborative – partnering with the Offices of Women's Health at the FDA and DHHS to develop prevention and cessation services, provide tobacco cessation materials, and provide regional and technical training for health centers staff.
- TB/Hepatitis C Health Disparities Elimination Project – collaborating with the Substance Abuse and Mental Health Services Administration and two types of CDC programs in selected health centers in three states to develop the infrastructure and models of care that facilitate TB and hepatitis C screening, prevention, and treatment strategies.

Summary

- HRSA supports programs in every U.S. state and territory.
- HRSA Community and HIV/AIDS Health Centers use sophisticated approaches to managing their patients to ensure adherence to clinical treatment guidelines for as many people as possible.
- HRSA is collaborating with others to develop model interventions based on guidelines and the evidence base that will enhance patient health outcomes.
- HRSA has a new Chief Public Health Officer, Dr. Kyu Rhee, who previously served in the NIH Center for Minority Health and Health Disparities and is helping to articulate HRSA's public health interests. Dr. Rhee has an interest in community based participatory research and comparative effectiveness research.

Committee Discussion

CFSAC members:

- Discussed how HRSA might become involved in developing CFS treatment guidelines.
- Noted that ARRA provided HRSA with hundreds of millions of dollars to improve access to care, a major issue for hundreds of thousands of CFS patients.
- Mentioned that the Agency for Healthcare Research and Quality (AHRQ) might also be helpful in developing CFS treatment guidelines since part of AHRQ's mandate is improving quality of care through disseminating guidelines to communities.

Dr. Willis-Fillinger:

- Explained that the focus areas for HRSA's community health center collaboratives are based on the disease burdens in those communities and the opportunities to use evidence-based clinical guidelines, standards of care, and performance measures to improve health outcomes. The challenge with CFS is identifying evidence-based steps that clinicians could take that would improve health outcomes.
- Noted that HRSA generally does not have a disease-specific focus. The agency has a legislative mandate for its involvement with HIV/AIDS. HRSA participates in the development of evidence-based guidelines for HIV/AIDS because there are resident experts within the agency and because HRSA has experience in managing HIV/AIDS patients. The role that the agency could play in developing CFS treatment guidelines is unclear.
- Suggested that CFSAC may want to schedule a presentation on the many avenues for guideline development.

- Noted that HRSA informed its Area Health Education Centers (AHECs) about the CDC CFS website and about the importance of CFS. It is up to entities within a community to request CFS training from the AHECs. Dr. Willis-Fillinger did not have information on whether the AHECs have received such requests.

CFSAC members also discussed the following topics:

- Several states have already developed CFS treatment guidelines. Any national standard-setting organization could draw from the best work that has already been done.
- The International Association of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS/ME) has expressed a willingness to collaborate with other groups on writing guidelines, but IACFS/ME lacks the funding.
- Writing treatment guidelines is not part of CFSAC's charter.
- CFSAC members would benefit from a presentation on guidelines development, including the role of AHRQ (which is due to produce an evidence-based state of the knowledge document by 2011) and the VA.

Dr. Jones said that CFSAC staff will research the agencies involved in developing treatment guidelines and invite them to the spring 2010 CFSAC meeting.

Public Comments

The following section highlights key points made by witnesses who testified during the public comment session. Access to the complete text of witnesses' written testimony is available at: <http://www.hhs.gov/advcomcfs/meetings/presentations/091029.html>.

Mike Dessin

I have experienced in my own life many of the challenges common to those who live with CFS:

The name—changed by the CDC from ME to CFS—minimizes the severity of symptoms and patient suffering and has attached a false stigma to the disease.

An ambulance tech told me on the way to the hospital after I collapsed in a New York City hotel lobby that there is no such thing as ME. I was placed in the psychiatric ward for 24 hours, quizzed about my personal life, and given a cocktail of psychiatric drugs. Shortly thereafter I went into a relapse that almost ended my life:

- I am nearly 6'3" and weighed 102 pounds.
- I had heart failure, severe pancreatitis, and collapsed lungs.
- I had extreme chemical and electromagnetic frequency sensitivities.

- I was unconscious 90% of the time during the last month before my recovery.

CFS patients lack special facilities with staff trained to care for ME/CFS patients.

I had spent 10 years searching for help from doctors and being told that my condition is JUST allergies, Epstein Barr, depression, or CFS. The medical community, family, and friends do not understand what is happening to CFS patients.

Funds for CFS research have dwindled over the years. The CDC spends research dollars studying cognitive behavioral therapy (CBT), psychological intervention, and graded exercise therapy as primary treatment and coping mechanisms. These therapies can be extremely dangerous unless they are integrated into treatment that addresses underlying issues.

Stress and depression in CFS patients is brought on by the severity of symptoms coupled with the lack of treatment and understanding of the disease. Due to abnormalities in the nervous system brought on by CFS, stress or depression can cause disease progression, just as with most other diseases.

Laurel Bertrand (testified via DVD due to her inability to travel)

I am unable to speak above a whisper because I have severe ME/CFS. My sister-in-law is reading my testimony for me. The CDC and NIH have failed us:

- They have not taken CFS seriously enough.
- They have not aggressively sought treatment and biomarkers.
- They have failed to inform the public and medical community that this disease can make a patient as sick as I am. I don't think that I would have become bedridden had I received proper education from my doctors. I was told just to push past it.

My personal story:

- I came down with CFS 13 years ago at age 24 after a severe bout of mononucleosis. I am bedridden, cannot leave the house, and have no real medical care.
- I graduated magna cum laude with a BS in psychology from Tufts University.
- My disease has nothing to do with depression of any kind.
- I found a companion online who has had a severe case of ME/CFS for 25 years and is wheelchair bound. He also developed CFS at a young age after a severe case of mononucleosis. Over the course of five years, we became best friends and fell in love. We are engaged and can't wait to be well enough to marry someday. We dream of having children and raising a family, traveling, having successful careers, and doing all the other things we've longed to do.
- Most of all, I dream of the vibrant, glorious feeling of good health and I strive for it everyday.

More needs to be done so that CFS patients can get their lives back:

- Raise money for biophysical research for a marker, treatment, or cure.
- Raise awareness so that those with CFS are not made to feel ashamed for being ill.
- Educate doctors so that patients are not dismissed or mistreated.
- Tighten the case definition of CFS and firm up research criteria.
- Change the name to one that doesn't trivialize the disease or simply focus on one of its many symptoms.

Laura A. Black

I am a healthcare provider dedicated to the treatment of CFS and other similar chronic diseases.

Over the last 25 years, the CDC has been funded with more than \$100 million but:

- The agency has made no effort to explore the many abnormal findings associated with CFS that have been discovered by researchers outside the CDC, including alterations of DNA and suspect viral infections or co-infections.
- Attempts to revise the original diagnostic criteria by relying on self-reported symptoms have grossly over-generalized the affected patient population and fueled controversy in the minds of many as to whether CFS is truly a physiologic and debilitating illness. Although there is no gold standard of diagnosis, there are enough physiologic biomarkers which have not even come into consideration with the revision of the diagnostic criteria.
- Diagnostic criteria need to be more specific and objective.
- Several therapies have shown potential in the treatment of CFS in small studies but lack the CDC funding to expand.
- The fact that after 25 years we do not have a single therapy approved by the FDA is unconscionable.
- Only 1000 hours of CME have been provided to healthcare professionals by the CDC.
- CFS is not spoken of in medical schools and residency programs, resulting in the inability of healthcare providers to properly diagnose and treat CFS.
- The \$9.1 billion economic impact of CFS is a large loss, but the even larger loss is the social cost of formerly productive citizens too sick to contribute and subject to psychological damage by abusive healthcare providers.
- There is no public health policy program at the CDC to counteract this ongoing stigmatization.
- Leadership at the CDC must change. The program has been insular and uninvolved with the larger scientific and patient communities. Leadership must treat CFS as an epidemic and a public health priority.

Kenneth Friedman

I am a medical school professor who has been asked by the IACFS/ME to comment on the status of CFS education in the United States.

The Academic and Medical School Environment

My employer's Director of the Office of Ethics and Compliance has informed me that my off-campus activities related to CFS are not part of my responsibilities as a university professor and may be punished with a penalty as severe as termination of my employment. I am not a unique target:

- One of my colleagues has left the same school.
- A different medical school has refused access to its students to discuss CFS or inform them of a scholarship.
- A statewide healthcare provider refuses to permit a CFS physician training session.
- The CDC has created this environment by failing to convince the medical establishment of the legitimacy of CFS.

Medical Student Education

- Were the CDC to mandate the reporting of CFS to the Federal government as it does for other illnesses, the National Board of Medical Examiners would have no choice but to put CFS questions on the National Boards and medical schools would have no choice but to include CFS in their curriculum.
- I have twice argued before CFSAC for the use of existing student programs within the NIH and the CDC to rotate medical students through NIH and CDC laboratories, but I have gotten no feedback on my proposal.
- The only mechanisms for educating medical students about CFS are the scholarship programs in three states run by patient advocacy groups.

CME for Physicians

- The CDC should mount a single national medical student program.
- The CDC's online CME CFS course has not increased the number of physicians who diagnose or treat CFS in Vermont, according to the Vermont CFIDS Association. The New Jersey CFS Association reports that the number of helpline requests for physician referrals has not diminished.

CFS Educational Materials

- All Federal and private sector literature concerning CFS is out of date. There is no mechanism for updating healthcare provider literature.
- I ask that CFSAC recommend that DHHS underwrite the expense of producing and distributing a national CFS diagnosis and treatment manual.

Deborah Waroff

My purpose is to discuss treatments for CFS that have been highly successful for me and are worthy of research dollars to learn more about the mechanism of the disease and to relieve the suffering of the nearly one million Americans whose lives have been ruined by CFS:

- The top treatment, which can obtain near-complete remission, is intravenous infusion of ozone done three to four times per week for 12 weeks. Intravenous ozone therapy is commonly used against pathogen-caused diseases in Russia, Poland, and Cuba where economics mitigate against high-priced pharmaceuticals. Ozone is legal in New York, among very few states. It should be legal everywhere. I went from being essentially bedridden to being able to walk, talk, get out and about, and write.
- A second treatment that succeeded in my case was a series of interventions involving dopaminergic and norepinephrinergic substances.

Lee Meisel

Two studies have brought CFS to a critical juncture in its history in terms of major research findings and the politics that could allow groundbreaking research to flourish:

- The publication in *Science Express* of the detection of XMRV in the blood cells of patients with CFS.
- The presentation of the valomaciclovir trial at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), marking the first in vivo demonstration of an anti-EBV effect of a drug in a phase 2, FDA-approved clinical trial.

Twenty-five years after the Lake Tahoe epidemic, we have finally built the foundation for CFS research to explode with innovative new findings, but we still lack ample research funding from the CDC and the NIH National Institute for Allergy and Infectious Diseases (NIAD):

- The CDC's five year CFS strategic plan and the levels of CFS research funding at NIH are an embarrassment.
- The CDC has failed to develop collaborative relationships with extramural researchers.
- The ideal clinical trial that studies the natural history of infectious mono as it morphs into CFS would be the perfect opportunity for the CDC and NIH to develop a study that would be truly transformative. Unfortunately the leadership of the agencies has not prioritized CFS research.

CFS patients deserve the same level of scientific rigor that has been applied to hepatitis C and HIV/AIDS. Such a program requires tremendous resources and technical

expertise, but the leadership at CDC and NIH has alienated a great number of the CFS stakeholders, patients, researchers, and clinicians.

A Congressional investigation is long overdue to explore potential allegations of malfeasance or potential misconduct at CDC.

It is time for the CDC and NIH CFS programs to be rebuilt from scratch, from the ground floor, with a new culture and new leadership.

Susan Magowitz

- I have had CFS and FM since 1995. After moving from New York to Atlanta, I have been unable to find a doctor who believes that CFS is a real illness. Replacing my CFS doctor has required four additional doctors plus a yearly return to New York City to see my CFS specialist.
- I have supraventricular tachycardia, shortness of breath, and high blood pressure. My doctors become irritated with me when they find no other heart problems and I insist my symptoms are CFS related.
- My endocrinologist simply ignores my CFS, although she does treat my Adult Onset Human Growth Hormone deficiency, Hashimoto's thyroiditis, and treats me with the same T3 and T4 combination prescribed by my CFS specialist.
- My pain doctor would not have accepted a CFS patient. My disc injuries are my diagnosis, so I can "document" my pain.
- Any one of my Georgia doctors would admit that I have some issues—my heart, my lungs, my endocrine system, and my neck and spinal cord injury. But like the blind men and the elephant, they would say I am reasonably healthy. Not one would mention CFS.
- I am here because I have the ability and resources to get here. My extensive medical history is pretty typical of CFS patients.
- No one warned me of the relapsing and remitting nature of the illness and I foolishly tried to exercise. It is time for the CDC to own up to its mistakes and start doing its job—warning us of the many dangers of CFS.

Megan Morgan-Shannon

- I became ill in the fall of 1982 as adeno-associated virus type 2 ran through Children's Hospital in San Diego. I was asked to leave my job because my immune system was compromised and I left in June 1983. I have been an activist for the past 20 years.
- I may appear well most of the time, but most of the time I am sick.
- I am requesting that all money that goes to both NIH and CDC go directly to the DHHS Office of Women's Health and CFSAC so that they can take over the duties of the CDC regarding education and research.
- Let us not make the mistake of changing the name of CFS—which focuses on one of the symptoms—to a name that focuses on one of the body systems such

as neuro endocrinology and immunological (NEIDS). This leaves out the cardiac system, a huge problem with this disease.

Harnoor Singh

I am a graduate student at the University of the Pacific. I have spent the last four years as a research assistant at the Pacific Fatigue Laboratory and as a scribe at the Emergency Department in the city of Modesto. Recently Joanne, a 50 year old small business owner, came to our research lab for a disability evaluation:

- Her long-term disability claim had been revoked. Her insurance company did not think she was sick.
- She had been dismissed by her local emergency room because an array of lab tests was inconclusive. Emergency room patients with CFS are often instructed to seek care from a primary care doctor.
- Many primary care doctors are not trained to consider CFS as a possible diagnosis. CFS patients are often considered malingerers.

There is hope if:

- Every member of the health care team is educated about CFS.
- Medical textbooks incorporate CFS to the same extent as other disease processes.
- Residency training consists of rotations in various centers for excellence in CFS diagnosis and treatment.
- Physicians are updated on groundbreaking treatments.

Eileen Holderman

I am a patient Advocate for ME/CFS. I would like to make three points:

1. I would like to endorse the document written by Dr. Kenneth Friedman, Marly Silverman and Rebecca Artman concerning the CDC's five year research plan and to endorse Dr. Dharam Ablashi's testimony given yesterday, especially as they relate to the need to investigate the role of infectious agents in ME/CFS.
2. We have to change the name of this disease, primarily because it correlates to funding. CFS doesn't sound medical, urgent, or deserving of funding.
3. The media's coverage of the discovery from the Whittemore Peterson Institute discourages me. The *New York Times* called the disease chronic fatigue several times. That is like isolating one symptom of diabetes and calling the disease chronic thirst syndrome, or dropping the "syndrome" and just calling the disease chronic thirst. It is so important to convey to the public the scientific nature of CFS. It will result in responsible reporting and subsequent research funding.

Federal health agency officials who address the media should receive coaching so that they can avoid buzz words that are hurtful.

Albert Donnay

I am an environmental health engineer and toxicologist who founded MCS Referral and Resources in 1994. My company has researched the overlap of CFS with FM, multiple chemical sensitivity, irritable bowel syndrome, etc.

I urge that CFSAC recommend to the DHHS Secretary and Dr. Kitt that researchers who are presumably interested in CFS are required to actually study CFS. The XMRV study did not assess the co-morbidities of patients with CFS or determine how many patients had pure CFS. I am not suggesting that DHHS dictate researchers' study design, but they should be required to assess co-morbidities and report results in terms of those co-morbidities. Otherwise we don't know if there's only one elephant in the room; maybe there are three elephants in the room.

Committee Discussion

Dr. Jones announced the distribution to committee members and the availability to the public of a listing of the 38 CFSAC recommendations made since 2004, sorted by focus area, agency, and progress. Eleven of the 38 recommendations show "yes" as a progress note, with another 10 showing "expected" progress.

Dr. Meisel informed **Dr. Papernik** that an abstract is available for the valomaciclovir presentation made by at ICAAC by Dr. Hank Balfour of the University of Minnesota. Dr. Jones said that her staff would place a link to the abstract on the CFSAC website.

Centers of Excellence

Committee members discussed how to review the 38 recommendations. **Dr. Oleske** noted that CFSAC has repeatedly recommended creation of CFS centers of excellence. **Dr. Klimas** commented that the recommendation appears repeatedly because of the very high level of importance that members have placed on centers. Dr. Oleske declared that when he steps down as CFSAC chair, if he could choose any recommendation for implementation, it would be CFS centers of excellence.

Dr. Jason suggested the importance of getting feedback from the DHHS Secretary's office on why the recommendation has not been implemented. Dr. Jones explained that when recommendations are transmitted to the Secretary's office, CFSAC has no control over their implementation and no feedback is required. The recommendations with affirmative progress are a tribute to the commitment of CFSAC's *ex officio* members. At committee members' urging, Dr. Jones agreed to try to arrange a meeting with the Secretary to discuss implementation of CFSAC recommendations.

Mr. Newfield expressed concern and frustration over the lack of feedback for the centers of excellence recommendation and the fact that no stimulus money has gone to CFS research. He urged that CFSAC continue to press for centers.

CFSAC Recommendation #1

Noting that private organizations like the Whittemore Peterson Institute cannot carry the research burden alone without government funding, Ms. Artman made a motion that CFSAC consider centers of excellence its number one priority in recommendations.

Dr. Snell agreed that the lack of feedback on recommendations inhibits CFSAC's effectiveness and leads to the committee repeatedly submitting the same recommendation.

Dr. Jason declared that the motion is heartfelt by both the patient and research community and that CFSAC wants a dialog about whether and how centers can or cannot be developed. **Ms. Healy** added that centers would also have an impact on provider education because they could offer training to healthcare professionals.

Dr. Bateman said that centers would address the committee's frustration with the research conducted by Federal agencies because centers would introduce healthy competition and professional interchange. She declared that centers of excellence would take a step toward solving almost every dilemma addressed by CFSAC. Ms. Artman added that centers would facilitate the sharing of patient data among researchers, create larger data sets, and accelerate the development of treatments.

Dr. Klimas noted that even if XMRV research continues to yield positive results, the CFS field does not have the infrastructure to put together a phase 3 clinical trial. Dr. Oleske pledged that if the motion passed, he and Dr. Jones would craft the recommendation to reflect the rapid development of clinical trial sites that could link together and conduct phase 3 studies. He said that the recommendation comes with the inherent need for CFSAC leadership to meet with the DHHS Secretary or her immediate designee to set the process in motion.

Dr. Jones clarified that the recommendation does not just rubberstamp what the committee has already approved but emphasizes that no matter what the next major finding may be, a research infrastructure must be in place to assemble patients through well-established networks to carry out necessary studies. Dr. Klimas further clarified that the network must be broad enough to also offer patients access to care and educate and train healthcare providers. Dr. Oleske reiterated that the "three legs of the stool"—teaching, education, and research—need to be reflected in the funded centers.

CFSAC unanimously passed Recommendation #1.

NIH RFA

Committee members next took up discussion of the release of another CFS RFA at NIH, which **Dr. Hanna** said would take place in fiscal year (FY) 2011. Several committee members noted that the release date will come five years after CFSAC passed the RFA recommendation and wondered if more immediate action could be taken to stimulate research. Dr. Jason asked Dr. Hanna to explain the timing of RFA development.

Dr. Hanna said that she must first get agreement from her director on a dollar amount for the RFA so that some research can be funded even if other institutes do not participate. A working group then develops the RFA, bringing it up to date with current knowledge by including background and posing questions for researchers to explore. Next the institutes sign on to fund research that is applicable to their work. The timeline for RFA development cannot be changed.

XMRV and Blood Safety and Availability

Dr. Oleske introduced Dr. Jerry Holmberg, who provided an explanation of blood bank safety issues in relation to the new information on viral isolation from the Whittemore Peterson Institute, including the issues of whether CFS patients should give blood and whether a method for rapid screening for XMRV is in development.

Jerry Holmberg, PhD, SBB, Senior Advisor for Blood Policy, *Blood Safety and Availability*, Office of Public Health and Science (OPHS)

Please note: The following section highlights key points made during the presentation. Access to any presentation text and accompanying documents is available at:
<http://www.hhs.gov/advcomcfs/meetings/presentations/091029.html>.

The Assistant Secretary for Health is the designated blood safety officer. The OPHS wants to make the blood supply as safe as possible. None of us wants to relive [the AIDS scare of] the early 1980s. My statement has been coordinated throughout all DHHS public health services.

- We are aware of the suggested linkage of CFS to a possible contagious rodent retrovirus, XMRV.
- Currently there is no commercially available test for infection with XMRV.
- While there is no known association of CFS with history of transfusion, the finding that the virus is associated with white blood cells has led some to question whether XMRV could be transmitted by transfusion and might therefore pose a threat to the health of blood and transplant recipients.
- The HHS Blood Safety Committee is taking steps to investigate the blood safety threat from XMRV. A report is expected by mid November.

- Investigators from the Retrovirus Epidemiology Donor Study (REDS) II at the NHLBI are assessing the prevalence of XMRV in blood donors to determine if studies aimed at the transfusion transmission rate are warranted.
- HHS will develop interventions as appropriate.

Committee Discussion

Dr. Klimas noted that the major scientific issue has been whether the tests for this new virus are accurate and asked Dr. Holmberg how confident he is that DHHS is using the best method possible. Dr. Holmberg explained that every test for screening blood, organs, and tissue has to go through the FDA process. The most sensitive way for testing for the virus is the nucleic acid process. He said that he is very comfortable that his team can think through the steps and coordinate public health service actions, especially given their history with the NHLBI Reds study.

Dr. Oleske expressed hope that OPHS would collaborate with the Whittemore Peterson Institute on addressing blood safety. Dr. Holmberg said that the emerging infectious disease group has already been in contact with the authors of that study and that there will be collaboration.

Dr. Oleske urged OPHS to take the lessons from the AIDS epidemic and not let competition and reputation become more important than protecting the blood bank.

Ms. Artman asked that a notice be posted on the CFSAC website—which is viewed worldwide—if OPHS determines that CFS patients should not give blood. Dr. Holmberg assured her that OPHS communicates effectively worldwide and collaborates with the World Health Organization.

Dr. Oleske noted that if CFS patients do not make up a crucial volume of the blood supply, perhaps they should be encouraged to avoid donating blood until an official policy is developed. Ms. Artman noted that the issue also encompasses organ donation and emphasized that she does not want to inadvertently cause others to suffer the way that she has suffered with CFS. Dr. Holmberg declined to make a statement about whether CFS patients should donate blood, noting that it is a personal choice. He suggested that those who decide not to donate can still recruit others to do so. He added that when policy is set on blood safety, a statement will appear on the FDA website.

Committee Discussion

CDC Five Year CFS Research Plan

Dr. Snell remarked that the five-year plan does not prioritize CDC research activities, adding that changes may be in order due to new major research developments.

Dr. Oleske asked **Dr. Miller** to comment on CFSAC CDC recommendations and how recent discoveries might affect CDC strategy. Dr. Miller said that he hopes the CDC will be able to make positive changes based on the Whittemore Peterson discovery, that the finding is confirmed, and that laboratories collaborate as a result. He said that he could not comment on exactly how the five year plan might be changed.

Dr. Snell said that CFSAC could recommend priorities within the five year plan. Dr. Miller said that the CDC was not charged to set priorities when it developed the plan because it is a broad strategic look at programs without the constraint of a budget. He also noted that the CDC does not know what its Congressional budget allocations will be over the next five years. Dr. Snell replied that CFSAC could recommend priorities no matter what the level of agency funding.

Dr. Miller reminded the committee that the initial work on XMRV is being led by the CDC retrovirus laboratory, not by the CFS laboratory.

Dr. Jason said the CFSAC Research Subcommittee recognizes that the funding that would be needed to implement everything in the CDC's five year plan would be excessive and that research priorities would be helpful in dealing with a limited budget. He asked Dr. Miller to elaborate on what happened to the CFSAC CDC recommendation from the committee's May 2009 meeting.

Dr. Miller replied that CFSAC recommendations are acted upon by the CDC regardless of whether the Secretary provides feedback, adding that the agency has never heard directly from the Secretary on any recommendations. He noted that no matter what CFSAC recommends, the CDC cannot increase its own funding, which is why some recommendations have not been acted upon.

Mr. Newfield requested an update on the CDC's intention to hold an international CFS workshop by winter 2009. Mr. Miller replied that the H1N1 flu epidemic has pushed that goal to a later date, but the agency still intends to hold a workshop.

Dr. Klimas inquired whether the CDC intends to research the development of persistent fatigue in post H1N1 patients. She also asked whether CDC will assemble another external peer review panel to examine the five year plan and how transparent the agency intends to be in setting research priorities. Dr. Miller said that the CDC intends to be completely transparent about research priorities but that he would have to check on the status of another external review. He added that he floated the proposal of a post H1N1 study to his program colleagues but that he would have to get back to Dr. Klimas with any developments.

Dr. Jones reminded committee members that their recommendations remain open until they are acted upon. Just because some have a "no" in the progress column does not mean that they will not be acted upon. She added that listing the recommendations in a handy reference format will help both CFSAC and Federal agencies to keep them in mind.

Surgeon General Letter

Committee members discussed whether it would be prudent to immediately approach the newly-confirmed SG, Dr. Regina Benjamin, to discuss a past CFSAC recommendation that the SG send a letter to healthcare providers and agencies nationwide informing them about CFS resources. **Dr. Papernik** advised waiting to see whether the XMRV studies are replicable and whether there are safety issues with the blood supply, noting that significant developments in either area would make the recommendation a more urgent priority.

Dr. Jones added that the SG's office is acutely aware of the XMRV and blood supply issues and is keen to advance CFSAC's work. The SG's office agrees that the best timing for a letter would be when more answers are forthcoming about these issues. **Dr. Klimas** reminded the committee that the pediatric case definition of CFS was also in the recommendation and would be an important part of the SG message.

Ms. Healy pointed out that many of the "yes" recommendations that involve communication with providers about CFS are one-time efforts. That is part of the issue CFSAC faces—these communications must be sustained efforts. Testimony has been given that provider information is not up to date nor are guidelines specific enough. CFS is not well known to the provider community. Communications have to be sustained, reiterated, and improved upon and CFSAC must find the HHS networks that are available to do so. It took the committee awhile to figure out that AHEC was a communication channel; there may be other networks over which information could be distributed.

[Dr. Oleske called a five minute break.]

Special Emphasis Panel

Dr. Cheryl Kitt, Deputy Director, Center for Scientific Review, NIH

Please note: The following section highlights key points made during the presentation. Access to any presentation text and accompanying documents is available at: <http://www.hhs.gov/advcomcfs/meetings/presentations/091029.html>.

CSR Peer Review: 2008 Statistics

- 77,000 applications were received.
- CSR used 16,000 reviewers from academia, business, and foundations. CFIDS gave CSR a list of potential reviewers and CSR will report within a year how many of those reviewers were used. CSR uses all reviewers who meet the qualifications and have no conflict of interest.

- CSR conducted 1,400 review meetings under the direction of 240 scientific review officers.

CSR Peer Review: 2009

2009 was an unprecedented year for CSR due to recovery act funding:

- 115,000 applications were received including 20,000 challenge grant program applications.
- CSR used 38,000 reviewers.
- CSR conducted 1,600 review meetings.

Former NIH Director Zerhouni had declared 2008 “The Year of Peer Review” in which CSR adjusted the process to incorporate the current trends in science and the efficiencies of the electronic age. CSR responded to the call to speed the funding of meritorious science and minimize the burden on reviewers:

- **Amended Applications.** As of January 25, 2009, the number of new amendments permitted for all original new applications and competing renewal applications will drop from two to one. Permitting two amendments resulted in few first-time applicants being funded because reviewers tended to ask for more application amendments. New or junior investigators were not able to wait.
- **Balanced and Fair Reviews Across Career Stages and Scientific Fields.** CSR has revamped the concept of **new investigator** (NI), which previously encompassed any investigator who has not received NIH funding. This definition resulted in senior scientists being classified as NIs. CSR now defines an **early stage investigator** (ESI) as one who qualifies as an NI *and* is within 10 years of completing a terminal research degree or is within 10 years of completing medical residency.

ESIs need to be identified so that they compete with each other during reviews rather than against senior investigators. This review break applies only to R01 grants. **The critical take home message:** ESIs should apply for R01 grants as soon as possible while the mandate to fund new investigators remains in effect.

- **Enhanced Review Criteria.** **The overall score** will be a percentile given in whole numbers and will be based on the likelihood of the project exerting a sustained, powerful influence on the field. The overall impact is scored from 1-9, but critique summary statements will score the impact between 10-90, with 10 being the best score.

Core criteria for scoring are significance, investigator(s), innovation, approach, and environment. All applications receive a score from 1-9 for each core criterion, including those who do not qualify for review by a study section. In previous years these applications were not scored.

Review scores will be given in whole number rather than decimal points because statisticians have advised CSR that whole numbers encourage reviewers to focus on the major differences between applications.

Reviewers discuss applications in the order of the average preliminary score, with the best score discussed first. This allows reviewers to more easily recalibrate and adjust scores during the discussion.

- **Critiques.** To improve quality and focus reviewer attention on the review criteria:
 - **Electronic critique templates** are categorized according to the strengths and weaknesses for each core criterion have replaced open ended critiques. Each criterion is allotted about one quarter of a page.
 - **Summary statements are shorter and more focused.**
 - **Only discussed applications** receive a summary of the panel's discussion.
 - **All applications are scored** but those applications that are not discussed receive criterion scores only.

- **Shortened Applications (beginning January 25, 2010)**
 - Applications for R01s will drop from 25 pages to 12 pages. R21 applications will drop from 15 pages to 6 pages.
 - Other mechanisms will be shortened appropriately.

All changes discussed can be viewed in the NIH Guide for Contracts, which is updated every week on the NIH website.

American Recovery and Reinvestment Act (ARRA)

In normal years, CSR receives about 16,000 applications for three review rounds. Due to ARRA funding, CSR received more than 40,000 applications for one round, including:

- 20,894 Challenge Applications
- 2,077 Competitive Revisions
- 2,697 GO (grant opportunity) grants
- 561 P 30

Many of the applicants were never funded before. ARRA stimulated interest from new investigators who will probably return to apply for more grants.

Still to be awarded under ARRA: "Building Sustainable Community-Linked Infrastructure," which has an application due date of December 11, 2009.

CFS Special Emphasis Panel

- Panel is permanent but members are not. This is due to the variety of scientific domains under which CFS applications fall.
- Panel is housed in the neuroscience division because that is the field in which most applications fall.
- CSR will continue to monitor applications to ensure that appropriate reviewers are chosen.
- CFSAC members should encourage colleagues to submit applications.
- The number of unsolicited CFS applications has not increased over the years. This may be because CFS grants are reviewed by panels in other fields, which raises the question of whether a CFS SEP is necessary.

Committee Discussion

Dr. Jason noted that the number of reviewers on the CFS SEP with appropriate expertise is increasing and congratulated Dr. Kitt for the progress. He delivered to her a letter from the IACFS/ME board of directors supporting continuation of the CFS SEP because of reviewers' expertise, noting that applicants always have the option of submitting their grants to other panels. Dr. Jason added that more expertise in biomarkers and virology is needed on the CFS SEP. Dr. Kitt urged applicants to specify in a cover letter where they want to be reviewed and the kind of expertise needed.

Dr. Klimas raised the issue of applicants facing a new set of reviewers when they resubmit their applications. Dr. Kitt replied that CSR does not guarantee the same reviewers and that the first priority is ensuring that the panel includes the appropriate expertise. She added that second round reviewers receive the summary statement from previous panels.

Dr. Jason noted that the 2005 CFS RFA stimulated a higher number of applications and that the upcoming RFA is likely to do so as well. He asked if there is any way for CFSAC to obtain data on the competitiveness of CFS grant applications (the number submitted and the number funded) as compared to other SEPs and study sections. Dr. Kitt replied that CSR could compile data and said that in general, applicants are more successful in SEPs than in study sections, and new investigators do better no matter where they apply.

Dr. Kitt recommended that senior scientists conduct workshops for new investigators on compiling successful applications, including how to handle reviewers' feedback. Dr. Jason noted that Dr. Hanna conducted such a workshop at the last IACFS/ME meeting. He added that the Research Subcommittee would like to discuss with Dr. Kitt variations in the review process, including conducting reviews by phone. Dr. Kitt said that the determination of whether to conduct reviews over the phone or in person is based on factors such as reviewers' schedules and number of applications. The goal is to get the best reviewers any way possible.

Dr. Jones announced that the previous day's final count for webcast views totaled 888.

[Subcommittee Lunch]

Discussion of Recommendations

Research Subcommittee Report/Recommendations

Dr. Jason, the subcommittee chair, maintained that the his panel could be more effective if members could conduct dialogs on a regular basis with the DHHS Secretary about CFSAC recommendations already made and what barriers blocked implementation of those in the “no” progress column.

Dr. Oleske noted that while committee members get frustrated that they are not doing as much as they would like, the group can be an avenue for the community, researchers, and funders. CFSAC meetings are one of few places where all three come together to discuss issues and express frustrations. Either the DHHS Secretary or a designee needs to attend a meeting to restate what their goals are for CFSAC and provide assurance that when the committee does put forth recommendations, they are at least being read.

Mr. Newfield asked that the DHHS Secretary's office carry out the commitment of Dr. John Agwunobi, former Assistant Secretary of Health, to attend at least every other CFSAC meeting. Dr. Oleske said that the level of the Secretary's commitment can be negotiated, but some presence would assure that her office is listening to CFSAC.

Dr. Jason said that his subcommittee members have had a continuing discussion about how CFSAC can make a difference in patients' access to healthcare, treatments, and an adequate number of physicians. Subcommittee work has focused on an infrastructure of support at NIH and CDC for research and empirically validated procedures. Subcommittee members are disappointed when they hear testimony every six months about patients' desperate situations. The subcommittee has hope that new research findings will make a difference.

Ms. Artman noted that even if XMRV turns out to be the marker for CFS, patients will still not have enough doctors who can treat the disease. The need for physicians is huge, pointing out that Dr. Klimas still has a three year waiting list. Ms. Artman declared that CFSAC must find a way to get new researchers and clinicians to treat CFS. Dr. Jason agreed that there is a crisis in the United States and business as usual is not acceptable.

Dr. Snell noted that all of the passionate testimony before CFSAC is heard by people who already understand the issues and that the greater public also needs to hear it. Dr.

Oleske thanked Dr. Jones for instituting the live web broadcast and the pod cast. He suggested that the news media might report on the meetings if they were informed about the story. If meeting participants give their permission, CFSAC could tell the news media about the pod cast. Dr. Oleske said that the testimony is compelling and there is a poignant story being told every meeting.

Mr. Newfield opened discussion about the fact that Dr. Oleske's term as CFSAC chair ends in January 2010 and expressed his desire to see Dr. Snell as the next chair. Dr. Jason also supported Dr. Snell as chair. **Dr. Jones** noted that Dr. Snell's term does not expire until April 2011. Ms. Artman suggested that since the CFSAC charter is being redone, the chair's term should be lengthened from two years to four years. Dr. Snell put forth the concept of having a "chair elect" so that the person chosen has advanced notice. **Dr. Klimas** expressed hope that the next chair would attend any meetings with the DHHS Secretary that Dr. Oleske arranges before his term expires. Dr. Oleske replied that he views such attendance as a must.

He continued that other CFSAC members may want to be the chair, noting that Dr. Klimas would also be an ideal committee leader. Dr. Oleske added that the current committee is a good mix of people, including those who are not members of the research or medical community. He cited Mr. Newfield, an attorney, and Ms. Artman, a patient advocate. Dr. Oleske said that new members should be of the same caliber as the current committee because CFSAC needs to be supported by the CFS community.

Education Subcommittee Report/Recommendations

Ms. Healy, the subcommittee chair, reported that her panel reviewed its previous recommendations and developed a new one:

CFSAC Recommendation #2

AHRQ is expected to complete a review of CFS for the NIH state of the knowledge workshop. After this process, the findings must be communicated to key medical education accreditation licensing boards, specialty boards, and certification organizations. In addition, the Surgeon General will develop a letter after the state of the knowledge meeting, as previously recommended by this committee, to better inform clinicians and other healthcare professionals throughout the United States and U.S. territories about the diagnosis and treatment of chronic fatigue syndrome in adults and children.

Ms. Healy said that the recommendation summarizes several important themes from the current and past CFSAC meetings, including Dr. Freidman's well-articulated description of the need to ensure that education about CFS is included in education for all clinicians whether they be physicians, physicians assistants, nurse practitioners, or other healthcare professionals.

Dr. Hanna said that the ARHQ report is delivered *at* the state of the science meeting, not before, and frames the final recommendations that are made, so CFSAC can not receive the report before the meeting. She added that the report is commissioned by NIH, so ARHQ would be doing the report for that agency. Dr. Hanna also noted that NIH has a new director and that the same report procedure may not apply.

Dr. Klimas pointed out that the recommendation addresses the issue raised by Dr. Freidman that board exam and accreditation bodies need evidence-based information about CFS. She advised that the recommendation needs teeth added to make sure that all information actually gets to where CFSAC wants it to go. She added that CFSAC needs to learn more about how board exams are developed.

Dr. Oleske said that the recommendation would be circulated to CFSAC members for further refinement.

CFSAC members unanimously passed Recommendation #2.

Patient Care/Quality of Life Subcommittee Report/Recommendations

Ms. Artman, the subcommittee chair, presented the following draft recommendation from her subcommittee:

In light of recent developments surrounding the suggested link between XMRV, we recommend the Secretary suspend the CDC's current CFS research program until results from the investigations into XMRV are available, including findings from the WPI and its collaborators, the Office of Public Health and Science's Blood Safety Committee, and the CDC's own Retroviral Laboratory. These research findings can then factor into a discussion of priorities and goals for the CDC's five year plan to include further consideration of case definition and the establishment of appropriate funding and leadership to achieve these goals.

Dr. Oleske expressed concern over a recommendation to suspend a whole research program rather than amending it to take XMRV findings into consideration and stressed that the CDC does a lot of good work. **Dr. Jones** noted that from a Federal budgetary standpoint, the funds must be expended even if the program is suspended. The danger is that the money would be directed elsewhere and then never recovered. She concluded that a program suspension is a serious activity that risks future funding altogether.

Dr. Oleske said that he wants to be firm with the CDC and ensure that it collaborates with the Whittemore Peterson Institute. He suggested a recommendation to amend the CDC's five-year plan to incorporate the XMRV virus. As angry as some have been about the CDC, said Dr. Oleske, 99 percent of agency employees work hard and are doing a wonderful job. He concluded that it is going too far to suspend the whole program because of anger over the inappropriate statements of one person.

Dr. Klimas noted that CFSAC passed a strongly worded statement at its May 2009 meeting asking for a change in leadership, and the result has been a five year plan with no provision for changing leadership. **Dr. Papernik** suggested that the DHHS Secretary is more likely to support a recommendation that prioritizes what research should be emphasized in the CDC's five year plan. He suggested amending the recommendation to state that the CDC should emphasize XMRV research until the virus's connection to CFS is proven or disproved. The emphasis should be on a viral approach.

Dr. Snell said CFSAC members mistrust current CDC leadership and do not feel confident that whatever happens with XMRV, it will be dealt with appropriately.

Ms. Artman explained that an earlier Quality of Life Subcommittee draft recommendation made four main points:

1. CFSAC asked for a change in CDC leadership and got a behind-the-scenes response in the lunch room as opposed to the official public response that was sought.
2. CFS requires a new case definition. There are currently multiple case definitions for CFS. CFSAC objects to a flawed version known as the empirical case definition. There are currently three other versions—the Fukuda and the Canadian Consensus definitions, which are used internationally, and the IACFS/ME pediatric case definition. The CDC should pursue a change in its diagnostic and research definition by referring to these better versions.
3. The subcommittee is concerned about Dr. Reeves' comments as a spokesperson for the CDC. He stated that he did not expect that he could validate the retrovirus and in predicting that he cannot do something, he may fulfill his own prophecy.
4. CFSAC should comprise the review panel to assess the CDC five year plan before it is implemented.

Ms. Artman said that the Quality of Life Subcommittee tried to write one recommendation that would address these multiple concerns. Members are frustrated and working to articulate their belief that big changes are needed at CDC. The subcommittee would like to hear feedback from the agency acknowledging that it needs a better CFS case definition and leadership that does not undermine other researchers.

Dr. Klimas said that while the subcommittee's draft recommendation may be extreme, it has directed attention to the frustration of trying to reshape the CDC research program time and again.

Ms. Artman withdrew her draft recommendation so that CFSAC could address each of the four points emphasized by her subcommittee in separate recommendations. Dr. Jason made a motion for a recommendation addressing the Quality of Life Subcommittee's first and third points:

CFSAC Recommendation #3

CFSAC is resubmitting the following recommendation as passed at the May 2009 meeting:

“Establish progressive leadership at the CDC that can achieve efficient meaningful progress in CFS research, clinical care, and education.”

CFSAC considers that recommendation important and would like to get some feedback, including whether or not the recommendation is being considered. This has become more important because of certain quotes that have been made in the *New York Times* concerning the retrovirus by the person in charge of the CDC program.

Dr. Oleske noted that the recommendation would be circulated to CFSAC members for further refinement.

CFSAC members unanimously passed Recommendation #3.

Ms. Artman read a proposed recommendation based on her subcommittee’s second point:

CFSAC Recommendation #4

There are multiple case definitions for CFS. It has been pointed out repeatedly at the CFSAC meetings. The CFSAC recommends that the CDC reject the empiric case definition and abandon the term “chronic unwellness.” There are currently two case definitions—the revised 2003 Fukuda definition and the Canadian Consensus definition—which are used internationally for diagnosis and research. Additionally, the IACFS/ME has a pediatric case definition. We ask that the CDC accept the other definitions.

Dr. Miller advised that the recommendation would be stronger if it included scientific references and supporting documentation. Dr. Oleske said that such background would be added.

CFSAC members unanimously passed Recommendation #4.

Ms. Artman read a proposed recommendation based on her subcommittee’s last concern:

CFSAC recommends that another external review group evaluates the five year plan as released in October 2009 by the CDC. We suggest that the review panel draw from the expertise of CFSAC members as part of this review panel.

CFSAC members discussed the fact that while the entire committee cannot be assigned the task of evaluating the CDC plan, the expertise of various members would contribute positively to such a review. Dr. Jason noted that a considerable number of people in

the U.S. scientific community have been dissatisfied with the composition of the external review group for the CDC CFS research program and have contended that the group did not conduct an unbiased review. He added that it is critical to select members of a second review group who do not have any conflict of interest with the CDC research team in Atlanta. Dr. Papernik suggested that such information be part of the recommendation to illustrate why another panel is needed.

Dr. Miller noted that the CDC asked for input from CFSAC on the five year plan and has gotten none. Dr. Klimas replied and Dr. Jones confirmed that acting as an advisor to CDC is not part of the CFSAC charter. Members were told that they had to make their comments individually and they have done so. Dr. Papernik added that CFSAC passed a recommendation at its May 2009 meeting asking the DHHS Secretary to provide adequate funding for the five year plan and setting out priority areas for progress.

Ms. Artman explained that the CDC's plan is not what Quality of Life Subcommittee members expected it to be. She said that members had planned to meet with Dr. Miller to discuss the plan, but were advised that such a meeting does not fall under the CFSAC charter.

Dr. Jason pointed out that details of the CDC plan had been available for just one week and there has not been time to address the many issues raised. The Research Subcommittee concluded that so many goals are mentioned in the plan that it would be difficult to accomplish them all. The CDC will spend the largest amount of money on CDC research in the world—\$25 million over five years—and it is critical that CFSAC feels comfortable with the direction of the plan.

Dr. Papernik said that the CDC plan is a good one, but not all parts can be accomplished. CFSAC members want to be sure that the emphasis is placed on the right parts of the plan. He maintained that having another panel review the plan is a waste of time. The issue is how to get across through the Secretary to the CDC that resources should be spent on the areas that CFSAC members deem important because they are the experts.

Dr. Bateman urged that CFSAC be specific about what items in the plan members would like to see happen. She was concerned that the broadness of the plan means that it cannot be fully accomplished. The CDC may try to make small, ineffective attempts to accomplish each goal, then say that the agency has met recommendations.

Dr. Papernik added that the committee is also concerned that the person heading CDC research will bend it to accomplish what he wants to do, not what CFSAC would like to see. Dr. Jones reminded members that it is in violation of their charter to attempt to control CDC research. Dr. Papernik replied that CFSAC wants the Secretary to direct where CDC research is going.

Mr. Newfield suggested that CFSAC reaffirm the recommendation from May 2009 supplemented with what the committee has learned since then. CSFAC expects the

Secretary to assure that the recommendations made in May are made priorities for the CDC five year research plan.

CFSAC Recommendation #5

Provide adequate funding to CDC to effectively carry out a detailed five-year plan. This should include, but not be limited to, immediate progress in these priority areas:

- 1. Identification of biomarkers including efforts in viral etiology of CFS;**
- 2. Creation of guidelines for adult and pediatric CFS management in full partnership with organizations representing CFS scientific and clinical expertise;**
- 3. Provision of web-based guidelines for CFS management given our current state of knowledge and expert opinion, again in full partnership with organizations representing CFS clinical and scientific expertise; and**
- 4. Provision of comprehensive information about CFS in partnership with CFS experts to the scientific community, medical and mental health providers, educational institutions and the public for both adult and pediatric CFS through DHHS resources.**

The recommendation has not been adequately captured in the CDC's five year CFS research plan and because of that, CFSAC must go back on record with what the committee sees as research priorities.

Dr. Oleske noted that the recommendation would be circulated to CFSAC members for further refinement.

CFSAC members unanimously passed Recommendation #5.

Dr. Miller said that he would take CFSAC's message back to his center director.

Comments from Outgoing Committee Members

Dr. Oleske

- Thanked CFSAC members for allowing a pediatrician to lead them.
- Expressed hope that the committee's work will lead to a wider recognition that children suffer from CFS.
- Thanked members of the CFS community for attending meetings and enduring until adjournment.
- Congratulated the Whittemore Peterson Institute and expressed hope that its discovery is the dawn of having etiologies that can be properly treated.

- Urged the committee to make sure that the DHHS Secretary or someone who directly represents her reads recommendations because they are important and should never be ignored.
- Declared that CDC is a wonderful place despite the committee's honest discussion about needed improvements.
- Expressed appreciation for all CFSAC *ex officio* members.
- Expressed appreciation to Dr. Jones and her staff and noted that she is more than just a support person—she understands the disease.

Ms. Artman

- Noted that she is submitting a final committee report.
- Advised that the best thing that CFSAC can do is provide tools to treat patients and help them get better. That is the purpose of research.
- Said that she is disheartened that more could not have been done about pediatric CFS, which will become her personal cause when her CFSAC term expires.
- Read a statement expressing horror that Georgia is allowing the CDC to study foster care children, who have already been traumatized enough.
- Expressed hope for the future and called for a stimulus package for medical care and science. She said that money for CFS research, treatment, and FDA drug trials is where an answer will be found to this illness.
- Expressed appreciation to CFS patients for their feedback and to CFSAC members for being a joy to serve with.

Dr. Bateman

Read a statement that:

- Described the background of her involvement with CFS, including the fact that her sister fell ill with the disease when Dr. Bateman was in medical school and died at age 51.
- Described the challenges of operating a private practice to treat CFS, including a significant reduction in income, the inability to provide her staff medical insurance, a clinic that generally runs in the red, and the necessity of moonlighting in drug research and consulting to pay her staff.
- Critiqued the CDC research program for denying a viral contribution and failing to understand the clinical subsets that meet the Fukuda CFS case definition.
- Asserted that NIH has not matched research funding to the significance of the problem.
- Thanked CFSAC members for their dedication.
- Expressed disappointment that the committee's repeated recommendations coming from those with the most CFS expertise have fallen on deaf ears.

- Expressed hope that recent progress in biomarker research will stimulate additional science that will place CFS patients in the mainstream of modern medicine.

Dr. Papernik

- Noted that he became a CFSAC member to be a patients' advocate and look for ways to make his patients' lives better.
- Declared that no matter where he goes in the United States, there are large numbers of patients who need help. CFSAC cannot stop looking for answers.
- Called the dedication of *ex officio* members has been an inspiration.
- Thanked the patients who attend and follow CFSAC meetings because "you keep reminding us why we're here."

Ms. Healy

- Described how she became involved with the CFS community in 1999 as part of the Illinois Area Education Health Center's CDC and CFIDS Association provider education project.
- Emphasized the value of provider education.
- Noted that her mission as an educator is to ensure that students learn about CFS.
- Described patient-centered care as an important aspect of healthcare and noted that unfortunately, CFS is an excellent way to teach that care.
- Expressed hope that she could continue to tell the patient stories that she has heard at CFSAC meetings over the years and continue to work with the CFS community to improve care in the future.
- Concluded that she has gained much more than she has contributed.

Dr. Jones:

- Noted that a link to the meeting pod cast will be placed on the CFSAC website.
- Encouraged the audience to suggest improvements.
- Described the meeting as an inspiration with a tremendous amount of encouragement and enthusiasm. "It feels like for the first time in quite a while we all have reason to be recharged and hopeful."
- Noted that the staff has "many wonderful applications" to review to replace the five departing members and expressed hope that the future group will have "a similar mix of expertise, passion, and compassion."
- Acknowledged the NIH web team and her staff and interns.
- Thanked the patient community and *ex officio* CFSAC members.
- Assured the public that all of their emails get read.
- Concluded that her office will announce new committee members shortly after the end-of-year holidays and the spring meeting date sometime in March 2009.

Dr. Jason thanked Dr. Oleske for keeping committee members cordial even during the tensest times, caring an incredible amount and being a tremendous leader.

Adjournment