CHRONIC FATIGUE SYNDROME ADVISORY COMMITTEE
Meeting

Monday, July 17, 2006
9:00 a.m. to 5:00 p.m.

Room 800, Hubert H. Humphrey Building
200 Independence Avenue, S.W.
Washington, D.C. 20201

Agenda

9:00 a.m.	**Call to Order** **Opening Remarks**	Dr. NahidMohagheghpour *Chair, CFSAC*
	Roll Call	Capt. David Rutstein *Acting Executive Secretary*
9:15 a.m.	**Federal Advisory Committee Act Briefing**	Patricia Mantoan *OGC Representative*
9:45 a.m.	**CFSAC Community/Organizational Updates**	Dr. Nancy Klimas *President, Internatl. Assoc. for CFS* Mr. Antonio Luna *Madrid's CFS Association*
10:30 a.m.	**Break**	
10:45 a.m.	**Updates from the Federal Sector**	*Ex-Officio* Members, CFSAC
12:00 Noon	**Lunch**	
1:00 p.m.	**Updates from the Federal Sector**	*Ex-Officio* Members, CFSAC
1:30 p.m.	**Department Leadership**	Dr. John O. Agwunobi Assistant Secretary for Health
2:00 p.m.	**Break**	
2:15 p.m.	**Committee Business/Discussion**	
4:15 p.m.	**Public Comments**	
4:45 p.m.	**Closing Remarks**	Dr. Nahid Mohagheghpour Capt. David Rutstein
5:00 p.m.	**Adjournment**	

U.S. Department of Health and Human Services

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Members in Attendance

CFS Advisory Committee Members

Chair
Dr. Nahid Mohagheghpour

Voting Members
Rebecca Artman
Dr. Lucinda Bateman
Jane Fitzpatrick
Dr. Kenneth Friedman
Kristine Healy
Dr. Anthony Komaroff
Jason Newfield
Dr. James Oleske
Dr. Morris Papernik
Staci Stevens

Ex Officio Members

Centers for Disease Control and Prevention (CDC)

Dr. William C. Reeves *(Primary)*
Chief, Viral Exanthems and Herpesvirus Branch
National Center for Infectious Diseases

Food and Drug Administration (FDA)

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

Health Resources and Services Administration (HRSA)

Dr. William A. Robinson
Director, Center for Quality

National Institutes of Health (NIH)

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

Social Security Administration (SSA)

Dr. Laurence Desi, Sr. *(Primary)*
Medical Officer
Office of Medical Policy

James Julian, Esq. *(Alternate)*
Director
Office of Medical Policy

Executive Secretary *(Acting)*

CAPT David Rutstein
Deputy Director
Office of Disease Prevention & Health Promotion

Invited Speakers

Patricia Mantoan, HHS Office of the General Counsel
Dr. Nancy Klimas, President, International Association for CFS
Antonio Luna, Madrid's CFS Association
Dr. John O. Agwunobi, HHS Assistant Secretary for Health

Call to Order, Opening Remarks

Dr. Anthony Komaroff

Dr. Komaroff chaired the first portion of the meeting for continuity's sake because CFS Advisory Committee Chair Dr. Nahid Mohagheghpour was not able to attend the previous meeting in April.

Roll Call

CAPT David Rutstein

CAPT Rutstein conducted roll call, noting that Voting Member Dr. James Oleske had not yet arrived. Dr. Oleske did take his place during the course of the meeting.

Federal Advisory Committee Act Briefing

Patricia Mantoan, *Representative, HHS Office of the General Counsel*
Accompanying Document: *Federal Advisory Committee Act*

Ms. Mantoan gave the committee an overview of the Federal Advisory Committee Act (FACA), which governs the formation of Federal advisory groups when membership in those groups is not limited to Federal government employees. FACA's purpose is to ensure the openness of advisory group activities so that Congress and the public are apprised of what takes place. FACA also creates standards of procedure for federal advisory committees:

- The committee must be advisory in nature. It is left to the discretion of Federal government officials or the President to take actions or make policy based on committee recommendations.
- Public meetings must be announced in an advance notice in the *Federal Register* 15 calendar days before the meeting. If a committee gives less notice, it must state why.
- Advisory committees must hold meetings in a room that will reasonably accommodate expected attendance. The public can give oral presentations if an agency's guidelines permit, or file written comments.
- Committees may formally close meetings when advice is given about grant applications because the Government in the Sunshine Act protects the privacy of competitive information. Committees must inform the public why they are closing such a meeting.
- Committee members may close a meeting without formal procedures when they are gathering information to prepare for an upcoming meeting or drafting position papers for committee deliberation. Members may also close a meeting without formal procedures if the meeting is convened solely to discuss administrative matters or receive administrative information from a federal officer, such as an ethics presentation.
- Subcommittee meetings are not necessarily required to be open to the public. A subcommittee is defined as two or more committee members meeting to gather

information for the committee, prepare draft position papers, etc. Subcommittees do not advise; they must present recommendations to the full committee to be discussed at a public meeting.
- Committee records must be made available to the public in a timely manner.
- The Freedom of Information Act requires that if a committee makes redactions in its records, it must note what type of information was redacted and why.
- Committees must provide detailed meeting minutes from a designated Federal official, usually the Executive Secretary of the committee.
- The Library of Congress must receive eight copies of any committee reports.

If a committee fails to adhere to FACA, the actions of the panel or its parent agency could be questioned, the agency may be barred from acting on committee recommendations, or the committee may have to start its advisory process all over again.

Committee Members Q&A

A question and answer session conducted by Ms. Mantoan with CFS Committee members yielded the following additional information:

- A committee has 90 days to certify the accuracy of meeting minutes. The committee chair is the person who must certify the meeting minutes' accuracy.
- The minutes should include only what happened at an actual committee meeting, not editorial comments added later.
- A committee's charter must be reviewed for renewal generally every two years. The CFS Advisory Committee last renewed its charter in August 2004, so it is up for renewal this year. The HHS Office of Public Health and Science will consider a two-year renewal for the CFS panel and make a recommendation to the HHS Secretary.
- Renewal criteria are based by law on whether an advisory panel has served a useful purpose for its parent agency.
- All members of Federal advisory committees receive ethics training, including those on panels whose charter is renewed.

Minutes

Committee members expressed concern about the April 2006 meeting minutes, which are not yet in final form. HHS staff members informed the committee that the vendor hired to produce the meeting report unexpectedly left the project. The minutes will be distributed via email for committee members' comments as soon as possible.

Moment of Silence

The committee held a moment of silence for former member Nelson Gantz, who passed away in late June 2006 after a long struggle with two debilitating illnesses.

CFSAC Community/Organizational Updates

Dr. Nancy Klimas, *President, International Association for CFS*

Dr. Klimas reported on the progress of CFS research, noting that in her 20th year as a researcher, solid evidence now exists to show that CFS is not affecting people in the United States by the tens of thousands as originally thought, but by the millions. According to Dr. Klimas, the scope of CFS is far wider than ever imagined, and the illness is a compelling area of research that gives her the very personal and privileged perspective of observing the courage of patients as they wait for a cure or advance in treatment.

CDC research shows that a family can lose half of its income due to CFS, said Dr. Klimas. Families are losing their houses and moving into trailers, losing trailers and moving in with aging parents, and then are being left out in cold when parents pass on. At the community level, patients often have no CFS expert in their state or even in a nearby state, according to Dr. Klimas. There are 80,000 CFS patients in Florida and she is the only CFS expert in her one-day-a-week clinic. Her next available appointment is in 2007.

The United States has failed tremendously in providing the clinical infrastructure to care for CFS patients, according to Dr. Klimas. The medical field is not training the next generation of physicians, nor is a critical mass of CFS investigators emerging—there have been no CFS training grants in 20 years. This, in turn, affects funding for research, because studies cannot take place if clinics cannot feed a critical mass of patients into clinical trials, including traditional R01-driven science, Dr. Klimas explained. Using the 1998 Wichita study, the CDC has calculated that only 15 percent of CFS cases are being diagnosed. Contributing to this low rate may be the fact that only those with the most severe symptoms seek medical help.

This lack of resources means that after 20 years of research, no natural history study with a broad patient base exists for CFS, continued Dr. Klimas. Researchers have not tracked what causes the death of CFS patients or what diseases affect them over the long term. Without such knowledge, the medical community cannot intervene to prevent at-risk illnesses. Researchers do not have CFS tissue, serum, DNA, or brain banks that are linked to a clinical data set, and there has been no mechanism for cataloguing and sharing samples held by individual investigators. Even as the number of CFS patients climbs, the number of published research studies has not increased.

Dr. Klimas predicted that the CFS research field would be reinvigorated by the creation of a large, well-funded clinic staffed by a multidisciplinary team. She told the Advisory Committee that researchers are not interested in studying CFS because there are 10 times the number of grant applicants as available grants.

A problem arises, however, because the number of CFS grants does not justify the formation of a standing review committee. This means that applications may not consistently receive reviews from the same panel. An investigator may submit an application, receive a low score, make suggested adjustments, then resubmit the application to a completely different set of reviewers. Dr. Klimas noted that such

conditions set up a negative cycle; that is, investigators hesitate to submit applications because they do not get consistent reviews.

Dr. Klimas provided a list of suggestions for increasing CFS research:

- An informal brainstorming meeting at NIH on how to attract a critical mass of investigators to the CFS field. Ideas from this meeting should evolve into a workshop, she suggested. CFS research should be able to ride the coattails of the NIH Roadmap's interdisciplinary approach rather than being hurt by it.
- Collection of data on research application scores—how are standing committees scoring grants versus special emphasis panels?
- Creation of clinical Centers of Excellence to provide clinical training and meet the needs of the 85 percent of CFS cases that go undiagnosed.
- Encouraging CFS investigators abroad in areas such as Europe, Australia, Japan, and New Zealand to propose Road Map initiatives. The density of investigators abroad is half that of the United States.

Antonio Luna, *Madrid's CFS Association (presentation by phone from Spain)*
Accompanying Document: *CFSAC Community/Organizational Updates*

Mr. Luna, whose wife is affected by CFS, described for the committee the state of CFS advocacy, research, and treatment in Spain, where organizations would like to create a worldwide synergy with other CFS groups, particularly those in the United States.

Mr. Luna noted that CFS is not even considered a disease in Spain and the government has no reservoir of knowledge about it. CFS is ignored by the current Administration, is not covered by Social Security, and only few research papers appear in peer-reviewed journals. Doctors spend only about five minutes per CFS patient and most lack medical protocols or guidance to help them diagnose the illness.

CFS patients face criticisms due to misconceptions, said Mr. Luna, including the idea that CFS is a psychological disease, and patients do not want to hold down a job or make an effort to improve. There is a lack of resources to train general practitioners (GPs)—which make up 90 percent of the medical community—to manage patients. CFS patients have a hard time getting disability and often seek a diagnosis of depression in order to qualify.

Mr. Luna told the Advisory Committee that politicians ignore the problem or take it into account only during election campaigns. Efforts to introduce propositions in Parliament, such as a 2002 measure to provide medical training, do not advance because the patient associations are not powerful and lack funding.

Spanish CFS patients are caught in a vicious cycle, according to Mr. Luna. Few private CFS specialists are members of the Scientific Panels that recommend that GPs manage CFS patients. Local and Federal health care agencies designate GPs as CFS managers, but provide no additional funding. Poor CFS management by GPs forces patients to travel to private specialists, and the cycle begins again.

Mr. Luna's association is promoting establishment of an Interdisciplinary Working Group in Spain to create a Consensus Document by the end of 2006 regarding CFS that will be accepted by medical societies. The Interdisciplinary Working Group will ideally have a representative from each of 10 specialties (immunology, psychology, etc.) so they can promote the Consensus Document to their peers, correct misconceptions, and establish protocols for diagnosing and treating CFS. The association also is seeking to publish articles in medical magazines.

The strategy to promote the Consensus Document throughout Spain includes meeting with members of Parliament and Social Security to educate government officials and promote programs and research, although funding is limited. The association is also publicizing its work to the mass media.

Luna proposed to the CFS Advisory Committee the establishment of a worldwide organization to create synergy among CFS organizations, avoid duplicating efforts, and make progress independent of the politics of any one country.

[Dr. Komaroff called a 15-minute break.]

Updates from the Federal Sector

Dr. William C. Reeves, CDC
Accompanying Document: *CDC CFS Activities as Related to Advisory Committee Recommendations*

Of the problems surrounding CFS that were noted by the Advisory Committee in its April 2004 recommendations, two of the most serious are the fact that there is no known cause or biologic marker to diagnose CFS and there is limited knowledge of the pathophysiology of the disease. As a result, up to 90 percent of CFS cases go undiagnosed and there is limited knowledge of effective treatment. The CDC is addressing these issues through provider education and through monitoring providers' knowledge, attitude, and beliefs and trying to change them.

Disability due to CFS has created a large national economic burden, said Dr. Reeves. The CDC has done the first studies of the economic impact and is refining its results to determine what is needed to plan effective intervention programs and a public health effort. Dr. Reeves also noted that CDC is developing standard guides to diagnose these disabilities.

The CFS Advisory Committee 2004 recommendations fell into four primary areas:

- Research efforts should apply an integrative approach.
- Research teams should be multidisciplinary – Dr. Reeves noted that CDC is taking an integrative, multi-disciplinary approach to its CFS work.
- Well-controlled, methodologically sound longitudinal studies are needed to clarify pathophysiology – Dr. Reeves said that CDC is uniquely able to do population-based studies that avoid the problems with clinically-based studies that Dr. Klimas noted in her presentation.

- Establishment of serum and tissue banks – Dr. Reeves listed several challenges with establishing such banks, including difficulties in documenting material, IRB issues with what material can be released, the exhaustion of materials used by single researchers in their own work, and the methodology of the people who want to use serum and tissue banks. He explained that not all studies are equally well designed and not all material in a given bank can answer the questions being posed by the studies.

Dr. Reeves then described what CDC is doing to follow specific Advisory Committee recommendations. He added that CDC is coordinating with other HHS agencies to carry out Committee advice. The first three Primary Recommendations call for:

1) **NIH development of five CFS-related Centers of Excellence.**
2) **An expedited NIH Request for Applications (RFA) on CFS with sufficient funds to attract senior researchers.**
3) **Development of an International Network of Collaboration to allow multidisciplinary research using standardized criteria, common protocols, and a large pool of patients from around the world.**

Dr. Reeves noted that the first two items are directed at NIH. As far as the third, CDC began such a network in 2000—the International CFS Study Group—which pulled together leading investigators from CDC, NIH, seven U.S. educational institutions, and eight institutions from six foreign nations, along with the leadership of the CFIDS Association of America. The Group held workshops between 2000-2003, with the first objective of defining what Group members thought were the most important CFS areas to be studied.

The Group conducted annual meetings, the result of which was publication of an article identifying ambiguities in the 1994 CFS research case definition and recommendations for their resolution. The Group has opted to publish its work in freely accessible peer review literature where it can be downloaded by any interested party.

The Group also recommended further study to determine if the construct of the case definition is correct. The 1994 definition was based on symptoms, said Dr. Reeves, and represents a consensus "of a bunch of people in a cigar smoked-filled room voting on what they thought comprised CFS". The International Group conducted a records review study comprising 22 countries and 50 sites within those countries that included almost 38,000 CFS patients. The Group looked at the data to determine if it could empirically compile a definition.

The core definition of CFS was found to be consistent across cultures, said Dr. Reeves. The key elements besides fatigue were cognition and sleep problems, musculoskeletal problems, and symptoms of inflammation or infection. The group also found that tertiary care was consistently unstable and skewed toward the particular setting (i.e., patients with neurological problems consulting neurologists, etc.). The manuscript presenting the multinational cross-cultural study results is currently under peer review.

The Group also met from 2003 through 2005 at CDC-sponsored three-day meetings at Banbury Center at the Cold Spring Harbor Laboratories, that pulled together international CFS experts as well as researchers not involved with CFS to approach the problems of defining biomarkers and the pathophysiology of the disease. The subject of

the first meeting in 2003 was understanding cellular and molecular mechanisms. The second meeting in 2004 covered compiling clinical, epidemiological, and gene expression data measured peripherally. The 2005 meeting on markers and models resulted in the recent publication in *Pharmacogenomics* of 14 papers on the core pathophysiology of CFS. The Group is contemplating an international workshop in 2007 on evaluation, diagnosis, and management of CFS. Dr. Reeves noted that the Group has collaborated at NIH with the Trans-Institute Working Group.

Dr. Reeves also reported on CDC progress in addressing the Advisory Committee's other Primary Recommendation:

4) **DHHS support and funding for an intramurally staffed laboratory committed to CFS research.**

He maintained that CDC operates such a laboratory that is just beginning to study cell functions and bioinformatics (i.e., how do you pull together this type of data on these sophisticated markers and apply it to an epidemiological problem?). The lab supports in-house as well as collaborative research, has heavy consultation, and engages in a large amount of technology transfer. The lab has trained Swedish, United Kingdom, and U.S. researchers. It is interested in studying how a wide variety of data contribute to CFS, including EEG and clinical data, gene expression profiles, genetics, apoptosis, and proteomics.

CDC is addressing the relevant Secondary Recommendations as well:

5) **DHHS encouragement and funding for CFS research related to children and adolescents.**

The CDC has published a variety of articles on CFS in adolescents and children. It is an extremely uncommon disease in people under 20, said Dr. Reeves. On the other hand, even if infrequent, CFS is a serious problem in children, because the illness affects them in years critical to their intellectual and social development. The CDC's Georgia surveillance study included children, and the agency is collaborating with researchers in the U.K. to develop a pediatric/adolescent case definition. The CFS patient registry, which the CDC should launch late this fiscal year or early next, is targeting children. Since CFS is a rarity in young people, population studies do not get at it, according to Dr. Reeves. However, researchers can access the cases of practitioners, so the CDC registry includes pediatric/adolescent healthcare givers.

6) **Continuation of DHHS workshops that focus on specific aspects of CFS and attract investigators who have an interest in but are not currently studying the illness.**

Dr. Reeves noted that CDC began integrating Advisory Committee recommendations as they are made rather than wait for DHHS to require implementation.

- In 2004, CDC sponsored three international meetings on CFS—one at the Psychoneuroimmunolgy Research Society, one at the International Society of Psychoneuroendocrinology, and an International Congress of Behavioral Medicine Workshop on new developments in CFS.

- The Banbury meetings—in addition to attracting CFS experts—have sparked interest in the disease among those in basic research.
- In May 2006, Duke University sponsored a competition in the critical assessment of micro array data using the Wichita clinical data set. One hundred papers were submitted; 10 were selected for presentation. Most researchers had never worked on CFS.
- Oak Ridge National Laboratory and the University of California-Los Angeles bioinformatics group are continuing collaborations with the CDC.
- In 2007, CDC will be doing a workshop on CFS at the Society of Behavioral Medicine Symposium.

To get researchers interested in CFS, they must become interested in the science behind it, concluded Dr. Reeves, and CDC meetings and workshops have gone a long way in sparking that interest.

7) Continued pursuit by DHHS of making CFS a training topic for health care providers and, wherever appropriate, at regional and national conferences.

Under a contract with the CFIDS Association, CDC is sponsoring a national training program for primary healthcare providers including physicians, nurse practitioners, and physician assistants. The free CME-accredited program is available on disk, video, and in print, according to Dr. Reeves.

- The CDC promotes the program through presentations and booths at national conferences whenever possible to educate practitioners about the evaluation, diagnosis, and management of CFS.
- The CDC makes grand round presentations at medical schools that have a family practice specialty.
- The agency has developed a CEU-accredited allied health professional education program aimed at chiropractors, physical and social therapists, massage therapists, etc.

Outcome measures are necessary to evaluate a program's effectiveness, noted Dr. Reeves. Currently in the works are:

- An evaluation of the "train the trainer" program that is in the final stages of peer review.
- A manuscript currently in preparation that evaluates the effectiveness of the CME-accredited training program for 2001-2006 and how it has changed practitioners' knowledge, attitudes, and beliefs.
- A CFIDS evaluation in the final stages of peer review that measures the knowledge, attitudes, and beliefs of practitioners nationally. Results will appear in a peer review journal so that the analysis is widely available.
- The CDC has just completed an urban area pilot study with 20 health care provider focus groups in Macon, Ga., that measured their knowledge, attitudes, and beliefs about CFS. The agency will conduct a similar evaluation of Macon's general population.

9) Increased public education about CFS by DHHS through a public awareness campaign.

Dr. Reeves reported that CDC is operating a contract with the CFIDS Association to conduct a national public awareness campaign tightly tied with the provider education effort. All have a common link on the CDC website.

10) Classification of CFS as a *Nervous System Disease* as worded in the ICD-10 G93.3

Dr. Reeves reported that there is no official CDC response to this Advisory Board recommendation. The research program technically believes that the classification is premature and that additional work is necessary in the areas outlined in his presentation.

Committee Members Q&A

Ms. Artman: How many participants have partaken in the CDC training program?

Dr. Reeves: Didn't put numbers in the talk, but it has been successful and the number of participants is increasing. More important than numbers is how effective it is. CDC is now at the point at which it can identify what creates a better outcome. The program is a national effort and it is difficult to measure changes in a national effort. That is why CDC will do intensive pilot work first in Macon, Ga., in a closed community, then tailor the national effort accordingly.

Dr. Mohagheghpour: Complimented CDC on the wealth of information presented in the program, expressed hope that DHHS will increase the funding, and commented that "it would be a tragedy" if the program lost momentum for lack of funding.

Ms. Fitzpatrick: In which peer review journal will outcome measures be published?

Dr. Reeves: Cannot reveal proposed publications for papers in peer review in case they do not pass publication standards. The CDC can specifically address education at the next Advisory Committee and present outcome measure results.

Ms. Fitzpatrick: Is the collaborative work with Oak Ridge/UCLA at the molecular level?

Dr. Reeves: They were both bioinformatics groups, but they were both interested in tying this together as a path of physiologic approach. They approached CFS in Canada as a purely computational exercise. When we saw their results and began talking to them about how we could potentially expand on this by bringing in much more clinical information, they got very interested. It is important to have researchers like the post-docs at Oak Ridge working on projects like this one. This particular data set is also the core of the bioinformatics program at NYU.

Ms. Artman: Do you have enough money to finish the Georgia study?

Dr. Reeves: There are two aspects to the Georgia study. One was the baseline study. What we need to do now is focus and get out the 10 analyses. Priority manuscripts are the prevalence analysis, access to and utilization of health care, economic impact analysis, and the case definition (does our finding in Georgia support our finding in Wichita?). We will probably within a year take the Georgia data as we have done with

other data and make it publicly available, but we need to get our prime hypotheses out first. The second round of funding for Georgia is in the final process of going through OMB. The second part of the longitudinal study is fully funded and will begin this year. The registry, which rounds this out, is also fully funded, so that will begin this year.

Dr. Papernik: Will the 2007 international meeting include the same researchers as past meetings?

Dr. Reeves: There's a core of international researchers in CFS, so some will be the same. Some have been identified specifically as interested in evaluation, diagnosis, and treatment, including those in the U.K. that are currently involved. The meeting is still in planning stages.

Dr. Friedman: Concerning the public awareness campaign – a scheduled press conference was not held. Some of the advertisements that include the new number of CFS cases have appeared. I and others are being put under pressure to explain how the new number was arrived at. I understand that papers are under peer review, but it puts me in awkward situation. Do you have any suggestions that might be beneficial?

Dr. Reeves: I have never been happy with the body count concept. It implies that we know the exact number of people who have something. Other diseases like cancer and AIDS can be pinpointed in the laboratory. With CFS, we are constrained by evaluating according to self-reporting by patients. CDC has been doing population surveys since 1992. As knowledge accumulates, we change what we do. Our first figures were from physician surveillance from their practices. They were very low estimates.

Then we began population-based studies. Initially people were screened for fatigue, then brought in for clinical evaluation under the 1994 case definition. The Wichita estimate was 300-500 per 100,000, or a million adults. This has been peer reviewed and replicated by another group.

As we have learned more, we understood that fatigue is not the only thing that bothers people with CFS. People also report, "I hurt; can't think clearly; feel crappy when I wake up." So we changed the screening algorithm to get people who are "unwell." It turns out that a substantial percentage of those with cognition problems have CFS. We cast a bigger and more sensitive net and got a larger number. We use a standardized instrument that would quantify the disability reported. There has been a rapid evolution in sensitivity and specificity in surveillance, so we have a new number.

The new number hasn't gone to a journal for peer review. When it is published with the evidence in a peer review journal, that is the appropriate time to announce in an open access journal so that people can evaluate. We are now in the stage of getting this finalized.

Dr. Mohagheghpour: Are you doing follow-ups in your population studies and if so, have you noted whether CFS runs in families?

Dr. Reeves: All of our studies are longitudinal in nature and not geared to looking at new cases within the same family. We did ask the household respondent to identify everyone in the house who's unwell and found it no more likely that two cases will be in the same CFS household than in the rest of population. There is no evidence in the

population basis of clustering in households. That is not easy to determine with a symptomatically defined illness.

Dr. Cavaille-Coll: Most protocols use the case definition from 1994. Do you have any recommendations about another kind of enrollment criteria?

Dr. Reeves: The International Collaborative Group does not believe that the verbatim 1994 case definition uses validated or accepted instruments to define fatigue, the disability associated with the fatigue, or the symptom complex. From our Wichita study, we believe that you really need to use replicable, validated criteria for diagnosis of CFS. We use the multidimensional fatigue inventory. There are others (SF 36; symptom inventory). None of this is static. We continue to develop. Without replicable manners of defining these things, you really can't measure clinical outcome. All instruments have been critiqued, but you do get the same results replicably in populations.

Ms. Healy: When will peer review be completed for the population data to be released?

Dr. Reeves: I believe it will be submitted for publication in early August.

Dr. Tony Komaroff: In regard to the *Pharmacogenomics* papers, which are incredibly difficult to obtain, is there any place to get free copies of them?

Dr. Reeves: No. They appear in *Pharmacogenomics* because it is available for free; they wanted the articles; the publication is very popular among pharmacologists, which I want to make an impact on; and I wasn't aware of the magazine's policy of making things available. People can ask me for individual pdf reprints. The text is not copyrighted; the format in which the journal publishes is the journal's intellectual property.

Dr. Tony Komaroff: The journal wants $350 for copies of all papers, which is a hardship on individuals and even some of the patient advocate organizations.

Ms. Artman: Is the CFS group homeless at CDC and is there a blue ribbon panel to figure out where you should be?

Dr. Reeves: CDC is in process of restructuring for approaching public health in 21st century. The first group reorganized has been Infectious Disease. The organizations within CDC of which we have been a part do not exist anymore. We have been having in-depth discussions about where we should really be, not just with respect to infectious diseases, but in the way that CDC approaches such things as CFS. It's a very overarching area—Gulf War illness was certainly a CFS-like disease, if not CFS. Symptoms that Hurricane Katrina survivors had were CFS-like problems. Dr. Cohen's question is, where should this be located overall in CDC? It is not a simple answer. He's considering putting together a blue ribbon panel of people from outside CDC with interest in CFS and similar illnesses, and within CDC to help determine where the best and most logical placement should be.

Dr. Komaroff: In response to committee recommendations, the CDC under your leadership has pulled a lot of investigators from around the world together, involved investigators who have never been interested in CFS in the past, and worked with methodological rigor. You have over the last three to four years amassed by far the

largest and most important body of knowledge about this illness that anyone or any group has yet done. It has changed the field. I just wish to thank you for that and I think it has implications for the recommendations from this committee on sustaining your momentum. I extend my personal thanks for an enormous and successful effort.

Dr. Reeves: It is not I. There is an entire group at CDC and internationally that has pulled this all together. They are completely dedicated.

Dr. Laurence Desi, Sr., SSA

8) DHHS should encourage continuing education for Social Security reviewers and adjudicators.

SSA continues to educate all adjudicators. We will be sending out notifications directing physicians to the CDC website to take advantage of the information there in addition to the CE credits. Even though many of the physicians are not clinicians in the way we use them—the medical consultants are not—the consultative examiners are, and this should help give them a better understanding of CFS.

CFS is an integral part of all the training that is going on within SSA as part of the new restructuring and business process of Social Security.

Committee Members Q&A

Ms. Healy: I had not heard that SSA was referring consulting examiners to the provider education project. Is that going to be a recommendation or are you going to mandate that they take part and measure outcomes?

Dr. Desi: We will encourage participation in the program. The medical consultants and consultative examiners work through the state system, so we can only encourage them.

James Julian, SSA Office of Medical Policy: There's an integration between SSA and the state agencies, which are the initial determiners of disability. Those determinations are done, by and large, by medical consultants. They are not full-time physicians working for the state or SSA. We encourage them to be, but we can't really require.

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

The Advisory Committee recommendations were not specific for FDA, but I can present new information on reviewing new drugs. This is a multidisciplinary process involving chemists, toxicologists, statisticians, clinicians, immunologists, and microbiologists. In September, the Center for Drug Evaluation and Research reorganized the Office of New Drugs. For the first time in more than a decade, all divisions of the Office of New Drugs are within same building instead of being scattered over five or six campuses. This has allowed us to interact with other disciplines and recognize that there is no single area of medicine that can claim CFS to its own.

Review of CFS drugs takes place within the newly named Division of Special Pathogen and Transplant Products. Given the kinds of tests used to evaluate CFS, however, such as exercise tolerance and endocrinologic tests, we are actively consulting with divisions with that expertise. That will enhance our ability to advise pharmaceutical companies that wish to investigate or design clinical trial programs in CFS.

What has not changed is that we continue to offer a program to help researchers who want to work with new investigational products to put together a successful I&D package that will get reviewed. We also continue to offer end of Phase 1 and end of Phase 2 meetings to look at data and help direct further research.

Committee Members Q&A

Dr. Komaroff: Are there any new pharmaceuticals for the treatment of CFS?

Dr. Cavaille-Coll: There are investigations of lawfully marketed products that do not require I&Ds and so we will not see those types of studies. As with AIDS before the pathophysiology and the virus was identified, it is difficult to screen pharmaceutical products that might show some promise. For screenings, there are usually animal or in vitro models—something is known about the pathophysiology that allows pharmaceutical companies to screen thousands of molecules before they begin testing. This remains an obstacle to CFS pharmaceuticals, which doesn't have such models.

Dr. William A. Robinson, Director, Center for Quality, HRSA

HRSA does not have dollars to directly support addressing this particular disease process. Programs are designed to improve the distribution of primary care services to people who have trouble accessing them. Some areas that indirectly encompass CFS are the Ryan White AIDS program, the network of comprehensive health centers (community, migrant), rural health programs, maternal/child health bureau (state block grants), and development of disaster preparedness plans for treatment of patient surge during a natural or manmade disaster.

One of our biggest programs has been reduced in the current budget and we're waiting to see what will happen with '07 budget—health professions training and education for primary care providers. We expect the funding to continue for nurses, however, which is the area with the most critical shortages. I look at this as an opportunity to continue working with Dr. Reeves' office and hopefully a little more closely with the CFIDS Association of America. I hope that Dr. Reeves will continue to get the necessary funding. The nursing profession has the single largest number of providers and is the most likely to interact with the largest number of patients across the board. We encourage that nurses be engaged in diagnosing and treating CFS, but we don't have the resources in our budget to help out.

The budget constrains HRSA from continuing to support such training for general internists and general pediatrics and family medicine practitioners based on what's happening with the budget.

[Dr. Komaroff called a break for lunch.]

Updates from the Federal Sector

Dr. Eleanor Hanna, Associate Director for Special Projects and Centers, Office of Research on Women's Health
Accompanying Document: "Chronic Fatigue Research at NIH"

Many of the activities of Dr. William Reeves' and his international team are due to NIH money and include NIH researchers. You can't divorce what NIH does from what CDC does. We [FDA, SSA, other agencies] do what we can within our missions to implement Committee recommendations. Also, last September I said that it's important for the Committee and advocates to keep in mind that the Federal enterprise is changing. NIH is up for reorganization. At least Dr. Reeves has a blue ribbon panel headed by his boss—NIH has Congress reauthorizing it. NIH used the example of CFS at a Congressional appropriations hearing to demonstrate what the NIH Roadmap can do to serve as a good example of what collaboration can do with no extra funding.

On the down side, all of the funding for any activity of the Trans-NIH Working Group comes from the budget of the Office of Research on Women's Health (ORWH). This unfortunately means that whatever we do for CFS means less money is spent on women's health research. In the four years that we've been doing this, we've made progress, although it's not moving as fast as we would like.

We are getting more grants coming in each round. We support investigator-initiated research. It is not all initiated by investigators, however, because they respond to NIH announcements. The only way to increase the CFS dollar amount that gets reported is to increase the number of research studies that we fund. That is the only dollar amount that NIH reports for CFS. I don't report my salary or meetings, just extra-mural research. There is some intramural research, but much of it is not counted because it's basic research.

Through 1999, NIAIDS had sole responsibility for the CFS program. In 1999, it was put in the Office of the Director so that CFS would more easily cross the spectrum of NIH Institutes. The Office of Women's Health engages in multidisciplinary and interdisciplinary research through the Trans-NIH Working Group (which has membership from 13 Institutes).

The Trans-NIH Working Group developed an action plan for CFS that first issued a program announcement to ensure that the effort was multidisciplinary and drew from people who were not already CFS researchers. The second step in the plan was announcing a small, scientific workshop designed to inform the direction of where we were going to go for the next 5-10 years. We selected neuro-immune mechanisms and CFS as a topic, hoping to piggyback on research available in brain science and immunology. Out of this workshop came establishment of a Special Interest Group on Scientific Integrative Medicine to promote intramural research.

An RFA was issued. Twenty-nine applications came in; seven have been encumbered. I cannot inform Advisory Committee what they are because only one has been formally announced by the Institutes. The RFA calls for an annual meeting of awardees at NIH. Through this meeting, we hope to develop research collaborations among people who

will then apply their work to Roadmap initiatives. The major task of the Working Group will be to plan for that annual meeting.

Other activities include:

- Working with professional societies to attract more researchers into Roadmap initiatives, the multidisciplinary clinical research centers, and all other activities that NIH is funding and that all Institutes have to pay into.
- Funding the original Lenny Jason epidemiologic study that showed that the CFS research base had to be broadened. He is also funded to do a follow up, so it will be like a natural history study in a population database.
- Funded the first large-scale population study from the Swedish twin registry. Many of these researchers are also members of Dr. Reeves' consortium.
- Funded a study on monozygotic twins that are discordant on CFS in order to look at the family hypothesis.
- Funded Baraniuk's work on the Gulf War and CFS in which he has developed an actual proteome. He's one of the people who is encumbered.
- Developed a huge portfolio in orthostatic tolerance.
- Presented the applications that will be reviewed for the next round of grants in August. Topics include stress, virus infection, and CFS.

Committee Members Q&A

Ms. Artman: Should CFS be located in the Office of Women's Health? Do you think that within the NIH that this is the best spot for it?

Dr. Hanna: Yes. The whole Roadmap—all of NIH's initiatives—are going to be trans-NIH, and everything is going to come out of the Director's office. This is one of the first things that was done this way. CFS was very well placed there. The Office of Research on Women's Health was the only NIH entity doing any trans-NIH research all of these years until Roadmap was conceived. Many of the ORWH Centers are models for the Roadmap Centers.

Dr. Komaroff: Have the number of applications spiked?

Dr. Hanna: They continue the upward trend, from zero in 2002, to at least 5 per round specific to CFS, for a total of 20 a year. Others are submitted for topics such as fibromyalgia that are also relevant to CFS.

Dr. Friedman: If Dr. Reeves' number ends up being the actual incidence of CFS, would that change your program?

Dr. Hanna: Not really, because if you're looking at the dollar figures, they result from the actual research that gets funded. It's not going to change the actual research that we're putting into the program. That would be beyond my pay grade to decide.

Dr. Friedman: If there has been an underestimate of the incidence of a serious disease with a significant economic impact by a factor of perhaps 4 or 5, wouldn't it be reasonable for the Federal government to ramp up its efforts to quantify, diagnose, and treat this illness?

Dr. Hanna: Yes, I couldn't agree more, but this is something beyond my pay grade.

Dr. Friedman: What should be done by this Committee? What should we recommend if the numbers end up being a four- to five-fold underestimate of the frequency of CFS?

Dr. Hanna: I think that if we continue these efforts with the scientific advances that now exist, we'll get there quickly. Some of the research that came into the RFA will lead to new treatment and so on. What Dr. Reeves is doing is phenomenal. NIH is going to continue to operate within its mission, and I don't know what this committee can do to change the mission of NIH.

Dr. Nahid Mohagheghpour introduced Dr. John O. Agwunobi, who was appointed by President Bush and reports directly to Secretary Mike Leavitt. Speaking extemporaneously, Dr. Agwunobi gave an overview of HHS's plans for the CFS Advisory Committee and took questions from the Committee.

Dr. John O. Agwunobi, Assistant Secretary for Health, HHS

I try to speak from the heart—I want you to get a sense of who I am and what I stand for. I am a pediatrician by training. I formally joined the Administration six months ago after serving as State Health Officer and Secretary for the Florida Department of Health for five years. Prior to that, I worked in Washington, D.C., in a small pediatric rehabilitation hospital called the Hospital for Sick Children, which handled pre- and post-op duties for children with neurological, orthopedic, severe cardiac, and gastro-intestinal disease. The hospital served as a long-term care facility for children with "orphan" diseases – those that are very rare, with skimpy science, and often no treatments. I was a "hospitalist" – I cared for children while they were being admitted to the facility and was assigned to communicate with and listen to parents and other family members.

I have relied since then on a skill that was taught to me in the middle of the night, typically –listening to the messages that the child was trying to deliver; listening to the message that the parent, grandparent, etc. was trying to deliver; listening to the language between child and caregiver; and trying to translate and articulate what I thought the problem was or what the solution was. The bottom line is that I learned to be a communicator—I learned the importance of listening and communicating.

I am the public health advisor to Secretary Leavitt, who is my kind of leader. He's a "thinker". He likes to learn the facts, go through a deliberative process that applies logic to those facts, and have options from which to select the best. I'm the "overseer of the public health service"—with no budgetary power, but a fair amount of influence due to the legacy of the prior structure of HHS. Prior to 1995, all of public health service agencies reported to the person who sat in my position and controlled policy and budget. Then-HHS Secretary Donna Shalella decided that agencies should report directly to the Secretary so that each would able to pursue its own missions and goals. One unintended consequence was that the public health service was pulled apart a little. Collaboration on cross-cutting issues such as CFS became a little more difficult to achieve.

My job without the power of the budget is to try to coordinate public health agency activities when I see the opportunity for one agency to help the other work toward the same goal. When I can see that offices can cooperate to achieve a department goal, I bring it to the Secretary's attention. I'm in the business of relationships—maintaining mine with the operational departments' leadership and those between each department.

I'm not so sure that we've done everything we can in the past to support this Advisory Committee's work. I have as a leader 918 days left on my term. I intend to make a tangible difference. I want to be measured by the things I have done, not the things I have said. There appears to be great opportunity for me to make a tangible difference in working with this Advisory Committee.

I am grateful for your service. I suspect that it's driven by your advocacy for the issue and your frustration that not enough is being done fast enough. I recognize that I find myself surrounded by advocates—thoughtful thinkers who want to make a difference. In that regard, I'm a kindred soul. I welcomed Jason Newfield as a new Committee member this morning. I swore him in about an hour before this meeting. He specializes in providing legal services to those with disabilities.

Prior to being Florida Secretary of Health, I served as Deputy Secretary for Children with Special Healthcare Needs and maintained clinics, advocated, and built case management for children with disabilities. I represent Secretary Leavitt here—he is in New Orleans chairing the committee to rebuild the post-Katrina health care system.

If something isn't working at HHS public health agencies, it isn't because of the people who work there. A lot of work has gone into the Committee's recommendations, and there's still a sense of dissatisfaction and a sense that much more needs to be done. I commend the work being done at NIH's Office of Research on Women's Health, and the CDC.

I think we need to realize that there are many syndromes and there are many diseases out there and they are all worthy of intense advocacy. Each is worthy of public awareness. But you have another level of awareness that we have to fight for every day. You still have to convince the institutions of the importance of this fight. Most other diseases and syndromes have gotten past that first step and are now fighting to convince the rest of the world. I recognize that that's one of the functions of this Advisory Committee—to push for awareness within the medical and public health infrastructure while making the broader public aware.

I want to talk about where we go from here. I need to be personally involved for 918 days and therefore make the following promises:

- ***I promise to attend more than half of your meetings in person.***

- ***I commit to making sure that you have a full-time Executive Secretary. By that I mean that the person may have other jobs to do, but you will have one person who works with you.***

- ***We have to re-charter this Committee—I commit to making sure this happens in an expeditious manner.*** Part of that process should also include the naming of members to the seats that might be open at that point. It should

also include the naming of a Chair. It's a great opportunity for us to rededicate ourselves to the mission, add new members if that's what's necessary, and identify a new chair if that's what's the will of the Committee and the will of the Secretary.

- There will be changes in science, policy, perhaps your priorities. As a part of this new charter, we should identify a recurring process through which you submit recommendations – reiterations of old ones, new ones, modifications to those already made. You need a standard process—annual report, biannual set of recommendations. I would urge the Committee to make it a calendared event so that at the end of any given period, there's an expected deliverable. ***My promise would be that whenever that deliverable arrives, it gets before the Secretary and a reply is delivered expeditiously. As a part of this chartering, we'll put together some sort of written response, including to the recommendations that you've already made.***

- The Administration wants to keep the cost of running the Federal government flat—not just HHS, but all agencies. We are currently developing the budget for '07 and '08 with this in mind. It's a tough time to ask for new money and build new programs in order to fulfill recommendations. Many agencies are having to figure out how to reprioritize within their programs. Having said that, ***where there are ways for us to push forward on the recommendations that may cost money, we will. We'll push them as far as we can.*** No doubt that the innovation in science and the innovation in policy that exists across this department can be used to further causes even in the absence of lots of new money. Don't restrict recommendations to that which we can afford—that's not your job. Your job is to say what you think the world needs to further this cause. Don't be frustrated if what you say needs to happen doesn't happen the next year.

Dr. Mohagheghpour thanked Dr. Agwunobi for "an enthusiastic and an honest" presentation. Dr. Komaroff called Dr. Agwunobi's remarks "music to my ears" and said he looks forward to seeing how they play out. The meeting was then opened to Committee Members Q&A.

Dr. Jane Fitzpatrick: What is the best way to bring primary healthcare providers up to speed when diagnosis has been problematic?

Dr. Agwunobi: There are three ways of moving health professionals and infrastructure toward CFS awareness:

- Money, such as insurance reimbursement of certain procedures.
- Science—if there's a best practice —is a more pressing motivator than money.
- More powerful than emerging science or an emerging funding stream is the demand of patients. An aware citizenry drives demand.

With any disease, there is a negotiation that occurs over time among patients, healthcare providers, science, funding, etc. A definition emerges that isn't quite where any one of the parties wanted it to be. Health funders want a narrow definition, science wants one absolutely defined by data that is verifiable and can be replicated, advocates

want a definition as broad as possible since nobody suffers from the same disease in the same way. The parameters shift over time as science and awareness grow. For CFS and the collection of syndromes under this umbrella, the final parameters will come about as a "negotiation", a development of consensus. As we move forward we should be open to all of the voices that we can.

Ms. Artman: The Secretary has a "500 Day Plan" and a "5,000 Day Plan". Should the Advisory Committee couch its recommendations in terms of what we'd like to see over a certain number of days?

Dr. Agwunobi: I think you need to be strategic. If you can, don't define recommendations according to any one Administration. This need is going to exist for a while. I would aim past the Administration—don't be restricted by our timeframe. But you should have some sense of how long it will take recommendations to be implemented. Consider time—how else will you be able to determine if recommendations are taking too long to be implemented?

Dr. Friedman: It is "almost criminal" that we still don't understand this disease enough to know how many people die of it. We should declare war on CFS by doing more than just funding grants in response to an RFA. Would the department be receptive if we were to be more creative than stimulating research through the channels that currently exist?

Dr. Agwunobi: The CDC report shows that there's a growing knowledge of CFS. The more we know, the better what needs to be done will be defined. I can only imagine that it adds an urgency to study, define, identify solutions. Don't let frustration push you away from the table. I'm sensing that the advocates over time are pushing us towards a place that wins the war against this disease.

Many a mistake has been made by surging toward a particular goal in the absence of data—in the absence of science—only to realize that it was the wrong direction. Join me in encouraging our scientists to continue that work. I know what you're saying…enough talk already, let's get the job done. I think that history will look back and say that if it weren't for your energy and passion, we wouldn't have gotten as far as we did. But I would urge a certain amount of patience with science.

Dr. Friedman: What will you take back to the Secretary from this meeting? How will you be able to convey not only our sentiments, but the nature of the illness itself? We are concerned that the Secretary doesn't really take it seriously and therefore puts it on the back burner. The data that our own scientists have come up with so far show that the illness is real and it's devastating. What can you take back that will garner support and funding for our scientists so that they can continue their work?

Dr. Agwunobi: I will tell the Secretary that I attended the Advisory Committee meeting and heard concern, frustration, passion, energy, urgency. I will tell him what I promised to the Committee. Discussing our written response to your recommendations is going to require a conversation of about 5-10 minutes. I would be lying if I said I was going to convert him overnight and he was going to become the number one CFS advocate. I will transmit back to you when I come back what he said, plus you'll have his written comments. Keep pushing, but don't be frustrated when you sense that you're not converting everyone to the same degree of advocacy.

Ms. Stevens: How can we retain the continuity of this committee? Half will rotate off in September and we have never had a permanent Executive Secretary—only acting.

Dr. Agwunobi: I promised you a permanent Executive Secretary. I heard that you haven't had a permanent one since Larry Fields. Ideally there shouldn't be a lot of time between each one. But there's also something to be said for members rotating out into the community so that they can talk to people about what's going on here. I'll be sure that in the new charter there are fresh voices, fresh perspectives, but that we overlap with some of the sitting members—a transition over time.

Audience question: The severity of the disease is illustrated by the death of my good friend's 23-year-old son Casey. He had myocarditis, but for years he was told that he "only" had chronic fatigue syndrome. All of the doctors at the University of Wisconsin Medical School were there for him and his parents were advocates. But too many people did not believe that it was a serious illness. For years his heart was eaten away by viruses until he died last year in his sleep at the age of 23. That's how severe this disease can be.

If we opened up the information process about this disease and weren't, for instance, stuck on the bio-psycho-social model, but opened up to all the avenues of information (neurology, immunology), the knowledge curve would skyrocket. People with this disease deserve that because for 20 years people have been sick—living in cars and on the street. No place to go and no medical treatment. This is a remarkably fascinating disease if looked at through the eyes of a fresh researcher.

Dr. Agwunobi: In the emergence of a new syndrome, there's frustration at the bottom of the curve where people are pushing to get it recognized and frustration at the top when it becomes well known and complacency sets in about moving quickly to find a cure. There is intense excitement in the middle when science starts to churn out work that's been in the pipeline for a while. I'm optimistic that if we continue this work, that eventually all of you will be holding your hats on as we speed up that curve and as things really fall into place.

Ms. Stevens: If there is no meeting in September, there will be no member who has been on this committee since its inception. I understand there are ways to extend the terms of a member or two for continuity.

Dr. Agwunobi: I'll speak to staff about the continuity problem. The key is obviously balance. It's about making sure that there's always opportunity for new voices and that over time we renew and regenerate.

Ms. Fitzpatrick: One thing that we've realized that we don't have any influence over—something economically important—is third party payers. They do really play a role for the patients who have this disease. Public relations and government influence does affect third party payers when the "experimental" label is removed from a treatment and a patient can get treatment plans recognized as something that must be reimbursed. There didn't seem to be a way for us to make recommendations to that end.

Dr. Agwunobi: Going back to the evolution of a disease into the mainstream—at some point there's no argument. It's in the transition before that that it's a matter of advocacy

to push the point and have it happen sooner rather than later. At some point it has to be covered. There are treatments, therefore they have to be covered; there are diagnostics, therefore they have to be covered. I would urge you to advise me and the Secretary of ways we can speed that up. I would also urge that you recognize that decisions made without science can work against you. If suddenly something else is shown by science that is different than the direction you went in, it undermines the credibility of the entire argument. There may be ways we can accelerate things, but I try to always have policy follow science.

[Dr. Mohagheghpour called a 20-minute coffee break.]

Dr. Mohagheghpour convened a ten-minute Committee discussion after Dr. Agwunobi's presentation.

Dr. Mohagheghpour: I'm very optimistic now because we finally received a message from the Administration. Dr. Agwunobi did bring some enthusiasm and hope to the meeting. Dr. Komaroff has volunteered to write a letter summarizing today's promises and activities of the Committee and suggesting that for sake of continuity, commissions of two members from the current Committee be extended. I fully support his suggestions.

Dr. Komaroff: I really wanted to focus on the progress that the Committee feels has been made in general and in specific actions relative to the recommendations we made two years ago. I'd like to summarize what we see as having happened and make the case primarily that it has generated momentum that we need to sustain, particularly at the CDC and at the NIH. The letter would be circulated through the Committee, then sent to the Secretary.

Dr. Hanna: If you're going to use the minutes from this meeting in any way, I'd like to clarify what Ken said. I think you misinterpreted my answer to you. I didn't say that I couldn't recommend what NIH should do; I said it's above my pay grade. What we are going to continue to do is what I said in my talk, and that is to take advantage of all funding opportunities that exist across NIH and use them as vehicles for CFS. It's the only way we're going to get what you want in the current budgetary state.

Dr. Friedman: I said that I was going to play the devil's advocate and appear ungrateful, but I am not ungrateful for what NIH does and continues to do. However, in the face of the situation and my own impatience, I would advocate and argue aggressively for more, and if there are budgetary constraints, then we need to find other ways around them. I'm sorry that you felt that I misused your statements. I was just trying to make clear the fact that it has been 20 years and the fact that even though there has been much progress—particularly now in view of the increased estimate of the magnitude of the problem—that we really need to do much more.

Dr. Hanna: I agree with you, but I also need to say that NIH hasn't been working on this as a multidisciplinary initiative for 20 years. It's only been since it was put in the Office of the Director. So you're really talking about the four or five years that I've been doing this with my committee.

Dr. Friedman made a formal motion that Dr. Komaroff compose a letter to be directed to the HHS Secretary that contains the status of research and implementation of Advisory Committee recommendations, what the Committee expects and anticipates in the future, and the importance of maintaining the momentum at the CDC and NIH. It was also suggested that the letter contain a request that the commissions of two members of the original Advisory Committee be continued for a short term to provide continuity to the committee.

The motion was seconded and passed.

Committee Business/Discussion

Continuity

Dr. Mohagheghpour led a discussion among Advisory Committee members about how to maintain continuity if the Administration does not agree to extend the terms of two panel members. Suggestions included**:**

- Ask a former Committee member to serve as an adviser.
- Extend the terms of two Committee members without seeking Administration approval because FACA permits former members to serve as consultants.
- Extend all members' terms for 90 days or until they have a replacement. This prompted a reading of the charter where it was discovered that any member may serve up to 180 days after the expiration of his/her term if a successor has not taken office.

A continuity motion/recommendation was deemed unnecessary.

Practitioner/Public Education and Review of Recommendations

Committee members next exchanged ideas for improving nurse/physician education and public awareness about CFS, and determining the proportion of CFS sufferers who receive treatment and how the disease affects their families. The ideas discussed included:

- Asking for a report from the CFIDS Association on the number of people being reached and how families are affected—particularly the caregivers.

- Supplying primary care providers with basic information on how to deal with patients who are afflicted with CFS. Providers currently have very little information on CFS diagnosis and its treatment and management. Even in the absence of definitive treatment, providers need guidance, and such information could be made available, including tools for correctly diagnosing CFS and advice on the day-to-day management of patients when knowledge about the physiology of their illness is scarce. Primary care providers hesitate to treat CFS because they don't know how to approach it, and yet there is a lot that can be done.

- Refining the goal for educating providers to go beyond merely teaching them how to diagnose and treat CFS to encompass evaluating ill people who exhibit fatigue

and the problems of CFS. Some patients may have other illnesses, or have CFS and be developing other illnesses.

- Circulating an email with more detail on provider education.

- Identifying large/key states and practitioners with CFS expertise, then providing educational opportunities to physicians. Key people in individual states would get the information to other people within that state.

- Forming a subcommittee to look into different aspects of provider education, then putting a proposal together via conference calls and/or emails. Preparing a proposal outline to review during the next meeting.

- Setting a timeline for resubmitting education recommendations as per Dr. Agwunobi's suggestion. Recommendations and potential revisions could be reviewed at the next CFSAC meeting with the idea that the Committee will resubmit them.

The idea of a new subcommittee review raised the idea that improving CFS education is a complex issue. Noting the work done by the previous education subcommittee, several Committee members pointed out that developing new recommendations might take up to six months.

The Committee considered a variety of ways to proceed with a review of the current status of CFS provider education. These included circulating the previous committee's report, calling for reports from ex-officio members on their progress and strategies for implementing previous recommendations, and calling for reports on provider education from outside organizations (Department of Veteran's Affairs, experts from the U.K.).

A major discussion point was whether to assign a new subcommittee to collect information and formulate recommendations, or have the Committee as a whole complete those tasks. Opinions ranged from producing new recommendations for review at the next meeting to using that time for an informational update and delaying creation of a new subcommittee until all members have been brought up to speed on what has already been accomplished with provider education.

The discussion also included two areas that some members suggested require further Committee attention: developing a physicians' manual on CFS and assuring that CFS is included in undergraduate medical education. Although its advisory status does not support the Committee developing a physicians' manual, members could recommend that such a document be created at the Federal level to provide more uniformity than the current process of each state developing its own manual. As far as including CFS in undergraduate education, the previous educational subcommittee reportedly approached and got no response from the AAMC or the American Medical Association.

The New Jersey CFS association was cited as a success story. The organization is establishing its own scholarship program at at least one of the state's medical schools and working with the Foundation of the University of Medicine and Dentistry to establish an endowment, which would rotate through all three medical schools. The point was

made that if one captures the attention of physicians in training, one has a better chance of influencing their attitude toward CFS as a bona fide illness.

Committee members reached agreement on how to approach educational issues for the next CFSAC meeting and discussed an appropriate date:

Dr. Reeves: I suggest that October would be a good time for the next meeting. By then a new charter would be in place and Committee members would know if they are returning or not.

In response to a suggestion that the meeting be held offsite at the ISCFS conference, **CAPT Rutstein** informed Committee members that this is not legal because they can't assure that FACA requirements would be met at an offsite facility.

Dr. Reeves: The Committee may want to make a presentation at the AACFS meeting about Advisory Committee activities.

Dr. Mohagheghpour: So, in preparation for the next Advisory Committee meeting, our previous education subcommittee report will be distributed to everyone. I will make sure that education is included in the next meeting agenda.

Dr. Reeves: I will supply documents about the undergraduate medical school scholarship program for the committee.

Ms. Artman: I would like to move that the meeting be held on either October 2 or 9—those are the first and second Mondays in October—and that the topic be education, and I would like to further move that the CDC, NIH, and HRSA also address what they see lacking in education so that we know what as a Committee we need to recommend.

Dr. Reeves: I second the motion.

[Discussion of date – October 2 is Yom Kippur; October 9 is Columbus Day. The next dates discussed were October 16 or 23. Members are checking on which date is convenient. Ms. Artman withdrew her motion for October 2 or 9.]

Ms. Stevens: What would be reasonable for members to expect for the turnaround of the minutes from this meeting so that we have them prior to next? As our Acting Executive Secretary, is that something that you can follow up on for us?

CAPT Rutstein: Yes.

Public Comments

Dr. Mohagheghpour: Members of the public will have 15 minutes to give their presentations.

Dr. Mary M. Schweitzer
Accompanying Document: ***Testimony to the Chronic Fatigue Syndrome Advisory Committee of the Department of Health and Human Services, Washington, D.C., July 17, 2006***

I thank the Committee members for their service and acknowledge that I and they have the same goal—to get to those who are sick with a very serious disease. I am not trying to be overly critical. When I attended the May 12 conference in London on Myalgic Encephalomyelitis, I learned that the diagnosis of CFS in England is according to a biopsychosocial model, which is to say that it is a diagnosis of being psychosomatic—a person gets sick with it and "forgets how to be well". Also, the Wessely definition used in England covers only "chronic fatigue" without encompassing the "syndrome", which quite dramatically dilutes the population. The result is studies that say cognitive therapy and exercise cure CFS.

The estimate of the number of CFS patients in the United States went from 500,000 in 1998 to four million eight years later. There are only a few options to explain this:

- A very big epidemic with a doubling every two years. In this case, I hope to see it on ABC News tonight.

- We have changed the definition. All along we've been watching it change and we haven't been paying attention. The CDC's website information on the research side now sends you to a list of publications about different case definitions. The last from the *Journal of Psychosomatic Research* notes that CFS is multidimensional and overlaps with other unexplained fatiguing syndromes. This definition blends CFS with other things. I'm worried that in doing so, instead of getting more specificity than Fukuda, we're going to lose specificity and have more of a heterogeneous population, which is going to make studies more difficult.

I'm also concerned that the direction we're going is the direction of the bio-psycho-social model. I maintain that the CDC's dataset no longer considers impaired cognitive functions or sleep abnormalities as major physical components of CFS. We are no longer using Fukuda. Questionnaires used by CDC are not easy to fill out and don't describe my disease well.

I am concerned about what is happening to patients under the Wessely definition, such as children being taken away from their parents because they aren't trying hard enough to get well. A 32 year-old woman was sent to a psychiatric hospital when she lost the ability to swallow. They tried to make her swallow, decided that she wasn't trying hard enough, and couldn't figure out why they couldn't make her. She died several months later from dehydration. The autopsy showed damage to the dorsal root ganglia. I would say that she died of misunderstanding due to the bio-psycho-social model. I do not want to see that migrate to the United States. I'd rather continue to do what we have been doing, and that is: continue to be a leader in using physical symptomology.

I urge the Committee to look toward the ME-CFS Canadian Consensus document—half of those who wrote it were from the United States—so that you can at least look at that for the possibility of modeling something.

Committee Q&A/Commentary

[?] There's another approach to why there are ballooning numbers—the way that people report data and that data is proved. Patients who had controlled thyroid and diabetes problems, or suffered from obesity or depression were not omitted from the

study. Also, Dr. Reeves noted that cognitive function and sleep problems were major components of CFS found worldwide.

Marly Silverman, Founder, P.A.N.D.O.R.A., Inc. (Patient Alliance for Neuroendocrineimmune Disorders Organization for Research and Advocacy
Accompanying Documents: Letter to CFS Advisory Board, discussion items for Dr. Agwunobi

I am very grateful that Dr. Agwunobi addressed every item in the letter that I sent to HSS Secretary Leavitt.

We are trying to establish a Center of Excellence in Florida because 60-75,000 people in the state meet the criteria for CFS and there is only one doctor—Dr. Klimas, who has a waiting list of two to three years. What is really the possibility of moving forward with that? I don't care what you call it (Center, Roadmap initiative), just do something about it. The quality of life issues are so important to people like me—they are the strength and fiber of the CFS community. It is important to have science to prove that this illness exists, but my job is to make sure that quality of life issues are addressed, and they're not.

You can be creative in this area. You cannot write a physicians manual, but you can suggest that grants be directed toward states to have a physicians' manual. Money is short, but Dr. Klimas treats CFS, fibromyalgia, and Gulf War syndrome, so with one dollar, you can kill three birds.

When we're talking about a national tissue bank, it may be that we need more than just one to open up to all the universities.

I invite Committee members to attend the 8th International IACFS Conference for Chronic Fatigue Syndrome, Fibromyalgia, and related illnesses, which P.A.N.D.O.R.A. will host on Jan. 10-14, 2007. The first two days will be a patient conference with an advocacy track that teaches media and presentation skills, including use of the Internet and lobbying.

K. Kimberly McCleary, President & CEO, CFIDS Association of America
Accompanying Document: *Updated Analysis of NIH-Funded Research on Chronic Fatigue Syndrome Shows Continued Trend of Diminishing Support, Fiscal Years 2000-2005*

For any CFS funding discussion, we should be looking at numbers with at least another zero added. Instead of talking about $6 million here and there, we should be talking about $60 million. But I thank Dr. Hanna, and I know that it's the work of the Office of Research on Women's Health that has pioneered trans-NIH initiatives in an organizational culture that doesn't have infrastructure for those kinds of things.

Funding is one quantifiable figure that we can look at over time to see where we're going. So many scientific advances are directly related to the financial investment

made in them. The Committee could also use the number of publications coming out of NIH programs to judge over time how well CFS is being addressed.

In 1998, the year of the CDC Inspector General (IG) report, the agency spent $2.2 million on CFS after the IG adjusted for funds that were actually directed elsewhere. By 2002, CDC was spending $11 million on CFS. You'll see in 2006 that the number is projected to drop from $9 million to $6 million and that is a great loss both to the efforts and to the momentum that has been generated over the last five years. I remind you that one Advisory Committee recommendation was to retain CFS funding at the 2005 level.

As Dr. Hanna reported earlier, in 1999 there were zero CFS grants submitted to NIH for review. During the RFA round with $4 million in funding, there were 29 proposals submitted a short time after the announcement. This demonstrates that when there is the investment of financial resources, there is a response from the scientific community. I also echo Tony's comments on keeping the momentum going at the CDC as well as riding on the coattails of the NIH RFA announcement.

In 2004, I contacted almost all of the lead researchers for NIH grants as well as some of the program officers because by title, many of the grants did not appear to be CFS-specific. At that time, my analysis showed that about 20% of what had been classified as CFS was actually unrelated or related to some other condition. If those figures are updated with the 2004-2005 list of grants provided to the House Appropriations Committee, that number rises to 36%. If some of these areas are relevant enough to CFS to count as CFS dollars, then NIH should have a process by which to transfer whatever knowledge we get from those grants to the CFS field. This needs to be done through more than just publication in a journal that someone working in the field may not know about.

I also suggest that the coding instructions that NIH has developed may be too broad. In September 2004, this Advisory Committee discussed the possibility of developing some relevancy criteria, and I don't think that action was ever taken. It might be appropriate for the Committee to advise the Department on coding instructions so that we have a consistent measure of things that should be counted as CFS over time.

A comment about the Reeves and Hanna workshops – the next generation of researchers and physicians isn't coming on their own, and we have to find them and recruit them into the study of this illness or there won't be enough people to repopulate this Committee or keep these various activities going. Too many people in the CFS field are reaching retirement age.

Closing Remarks

CAPT Rutstein: I thank the Committee for its efforts, particularly those members about to rotate off, on behalf of myself, John Eckhardt, Dr. Agwunobi, and Secretary Leavitt. Thank you for your tolerance and patience in putting up with the way this Committee is managed. I'm heartened by Admiral Agwunobi's comments, and I would suggest that the horizon is bright for the future of this Committee. I think you can be assured that the management of this Committee—including a permanent Executive Secretary—will be

forthcoming and be improved. Thank you to Olga Nelson, who works tirelessly in a completely understaffed, under sourced way to make the arrangements for you.

Adjournment of Committee Meeting – Dr. Nahid Mohagheghpour, Chair