

THE CFIDS ASSOCIATION OF AMERICA

THE CFS RESEARCH REVIEW

Providing up-to-date
information on
research, diagnosis and
treatment of CFS for
medical professionals

WINTER 2005 ■ VOLUME 6 ISSUE 1

AACFS Hosts Three-Day Conference

By Charles W. Lapp, M.D.

Conference Overview

The Seventh International Conference on Chronic Fatigue Syndrome, Fibromyalgia and Other Related Illnesses was held October 8-10, 2004, in beautiful Madison, Wisconsin.

Cosponsored by the AACFS (American Association of Chronic Fatigue Syndrome) and the CDC (Centers for Disease Control and Prevention), this year's conference attracted 235 attendees, 39 of whom came from overseas. In addition to the United States, fifteen countries were represented: Spain, New Zealand, Australia, Belgium, Canada, France, Ireland, Sweden, the Netherlands, Italy, Denmark, Norway, Japan, Korea and Mexico. More than half the attendees were medical professionals; the balance were mostly patients and caregivers.

One hundred forty-five abstracts were submitted to the organization committee. The final scientific program consisted of 48 scientific presentations, five reviews, two philosophical approaches and four workshops. More than 75 posters were available for review between sessions.

Drs. Leonard Jason, Dharam Ablashi and Lucinda Bateman contributed extensively as the program organizers; Drs. Daniel Clauw and Kenny De Meirleir co-chaired the research section; while Dr. Stanley Schwartz and I headed the clinical section. AACFS board members Patricia Fennel, Lyle Lieberman and Drs. Birgitta Evengard, Hirohiko Kuratsune, Benjamin Natelson and Nancy Klimas also contributed to the smooth execution

of the conference.

Overall the conference was a great success. The research track was superb, providing new material and approaches for the understanding and diagnosis of CFS and FM. I am confident that many researchers and clinicians left this session with new and exciting ideas. I was impressed by Dr. Anthony Komaroff's overview of CFS/FM achievements in the past two years, and by Dr. William Reeves's all-encompassing epidemiology review, which summarized the CDC experience over the past few years.

Most clinicians were overwhelmingly pleased with the clinical track, which focused mostly on specific areas where treatment modalities exist and have been successful. These were dysautonomias and orthostatic intolerance, low-level progressive exercise and behavioral therapy. Three mini-seminars highlighted these areas, and providers left the sessions feeling enthusiastic and armed with new approaches to share with their patients.

As in the past, I was disappointed with the lack of new papers on treatment. Only one paper (on Ampligen) specifically dealt with treatment, although several others dealt with the approach to CFS or FM.

It's my hope that the next conference will emphasize therapy by highlighting specific treatment areas such as sleep, pain and hormonal therapies and will include a lengthy open forum for clinicians to exchange ideas. ■

SPECIAL EDITION

This issue is entirely dedicated to the October 2004 AACFS conference. A collaborative project of the CFIDS Association of America and the American Association of Chronic Fatigue Syndrome (AACFS), this issue was funded by an education grant from the AACFS. Our thanks go to the entire AACFS board for their support of this project.

INSIDE

Patient Section
2

Research Section
4

Clinical Section
8

Clinical Workshops
12

Membership Form
16

THE CFS* RESEARCH REVIEW

The CFIDS Association
of America President & CEO
K. Kimberly McCleary

Director of Communications
Marcia Harmon

Editor
Angenette Rice-Figueroa

Editorial Advisory Board
Mary Ann Fletcher, Ph.D.
Professor of Medicine
and Microbiology, and
Director of the EM Paper
Laboratory of Clinical Immunology,
University of Miami
School of Medicine
Miami, FL

Terry Hedrick, Ph.D.
CFS Patient, Research
Methodologist
Cobb Island, MD

Leonard Jason, Ph.D.
Professor of Psychology
DePaul University
Chicago, IL

Charles Lapp, M.D.
Clinical Associate Professor
of Family and Community
Medicine, Duke University; and
Director, Hunter-Hopkins Center
Charlotte, NC

Paul H. Levine, M.D.
Clinical Professor of Epidemiology
and Biostatistics, the George
Washington School of Public
Health and Health Services, and
Clinical Professor of Medicine,
the George Washington
University School of Medicine
Washington, DC

Nancy Reichenbach
Associate Scientist
Department of Biochemistry
Temple University
School of Medicine
Philadelphia, PA

Charles Shepherd, M.D.
Medical Director
ME Association
Essex, England

*Chronic fatigue syndrome
(CFS) is also known as chronic
fatigue and immune dysfunction
syndrome (CFIDS) or myalgic
encephalomyelitis (ME).

The CFS Research Review is published by the CFIDS Association of America, PO Box 220398, Charlotte, NC 28222; telephone 704-365-2343.

The CFIDS Association of America does not endorse products or services, and the ideas expressed belong strictly to the authors, not the Association or the CFS Research Review. The Association and the CFS Research Review assume no liability for any medical treatment or other activity undertaken by readers.

© Copyright 2005 by the CFIDS Association of America.

Patient Section

Saturday, October 9 - Sunday, October 10

By Nancy Klimas, M.D.

The patient section of the AACFS conference was well-received by patients and family members. Chaired by Dr. Dharam Ablashi and I, the conference committee included Kim McCleary, Pat Fero, Patricia Fennell, Dr. Leonard Jason and Lyle Leiberman. Together, we developed an agenda that was both informative and experiential.

The conference began with a welcome by Ablashi, who noted that the entire purpose of the AACFS is to improve the life of CFS and FM patients through research, better clinical care and advocacy.

We continued with a panel on "Matching Best Medical Practices to Phases of Illness: An Integrated Panel Discussion with Physicians and Allied Health Professionals." I moderated the panel with Patricia Fennell, Dr. Lucinda Bateman and Dr. Susan Levine. Fennell identified four progressive phases of change—crisis, stabilization, resolution and integration—that occur for nearly everyone dealing with chronic illnesses such as CFS. She described effective psychological strategies that can enable chronically ill patients to live their lives to the fullest, and then asked fellow panelists to describe the current medical practices that would be used in each phase of illness.

Staci Stevens presented a practical workshop on effective exercise programs for CFS and FM patients. Because too much exercise leads to relapse, Stevens has worked out effective exercise strategies that build slowly to form a realistic baseline. Her program emphasizes stretching, strength building and gradual increases in aerobic conditioning, with rest periods and a plan for managing CFS/FM flare-ups over time.

Pat Fero, the executive director of the Wisconsin CFS Association, put together a diverse set of experiential workshops for the



The advocacy workshop included panelists John Herd, Kim McCleary and Rebecca Artman (pictured), as well as Pat Fero and Jill McLaughlin (not pictured).

Saturday breakout sessions. These included tai chi, massage, yoga, meditation, art therapy and qigong. Throughout the three-day conference, there was a fully stocked art studio where patients tried out various ways to express themselves. Local artists with CFS also displayed their work.

The final day of the patient track began with my research update. I incorporated the most current information that had been reported in the first two days of the conference and reviewed the basic science of CFS, how it has led to clinical studies and how the science is impacting more focused clinical interventions in CFS.

Next, Fennell led an Oprah-style roundtable on "Sex, Socializing and Sleep: Night and Day with CFS," where patients, spouses and panelists talked about issues of intimacy and daily life in a CFS household. Panelists (Jason, Dr. Daniel Peterson and myself) may have learned as much as we taught that day since audience members gave frank advice to each other and to those of us on the panel.

Open interchange was the model of the patient section, with an outstanding luncheon give-and-take discussion with disability expert Tom Bush. He urged the participants not to give up on the system, but to approach disability issues in an organized

and well-documented fashion, preferably with counsel. He noted that the process is a long one, but persistence pays off.

On Sunday afternoon patients, clinicians and scientists joined together for an advocacy workshop, "From Grassroots to Action." This session included activists from the medical community and the patient advocacy community, who took questions from the large audience. Moderated by Fero and Kim McCleary, CEO of the CFIDS Association of America, the workshop helped build coalitions among the advocacy groups represented by the panelists.

We ended the conference with a briefing on the Department of Health and Human Services CFS Advisory Committee (CFSAC). Dr. David Bell reported that the committee has done some amazing work in its first year, forwarding a list of recommendations to the Secretary of Health that, if implemented, would result in improved research funding, more education of clinicians and the public, and better services from governmental agencies such as the Social Security Administration. Ablashi thanked the conference organizers and participants for what was a highly successful conference and charged each of us with the task of continuing our advocacy involvement. ■

AACFS AWARDS PRESENTED AT BANQUET

The traditional awards banquet was held Saturday night at the Alliant Energy Conference Center and was well attended. Following a superb dinner and polka music, Dr. Dharam Ablashi, president of the AACFS, presided over the awards ceremony.

The AACFS's most coveted award—the Rudy Perpich Memorial Award—went to Dr. Dedra Buchwald, director of the Chronic Fatigue Clinic at Harborview Medical Center in Seattle. The award was presented by Dr. Tony Komaroff, whom Buchwald worked with at Harvard, where she assisted him in investigating the 1983 CFS epidemic at Lake Tahoe. Since that time Buchwald has been a staunch supporter of PWCs, a former AACFS president, a prolific researcher and writer, and head of the National CFS Twin Registry. Buchwald entertained banquet attendees with her own version of *This Is Your Life*.



The Junior Investigator Award recipient was Susan Torres-Harding, Ph.D., of DePaul University in Chicago. This award was presented by Dr. Stanley Schwartz, and followed by a touching acceptance speech by Torres-Harding, who was initially drawn to our field when a Spanish-speaking psychologist was needed for CFS studies being performed in Chicago. Torres-Harding is now a project director for CFS investigations at DePaul.



A Special Service Award was presented to Judy Basso, founder of the Minnesota CFS/FM Association, for her fervent work with the late Governor Rudy Perpich and others to further understanding of CFS/FM and promote medical care for sufferers.



The last Special Service Award recipient was Christine Hunter, who traveled from Sydney, Australia, to attend the conference and accept this accolade. Hunter's daughter, Alison, died of complications of CFS in 1996. After Alison's death, Christine started the Alison Hunter Memorial Foundation (AHMF), a nonprofit institution that works independently with researchers, institutions and ME/CFS societies to advance scientific knowledge and medical care. The foundation has been extremely effective with respect to advocacy, patient support and education. Hunter almost single-handedly produced three international conferences in Sydney (1998, 1999 and 2001)—conferences that have facilitated the networking of researchers and clinicians worldwide. The award was presented by Dr. Charles Lapp, who knew the Hunter family well and even named his Charlotte clinic in honor of Alison.



Research Section

Friday, October 8

By Charles W. Lapp, M.D. **CFS/FM research overview**

Dr. Anthony Komaroff of Harvard School of Medicine kicked off the research section, as usual, with an excellent overview of research conducted during the past two years. His much-anticipated summary of study findings included these key points:

- The Medical Outcome Study Short Form-36 is a reliable, validated survey that has shown substantial reductions in function in people with CFS (PWCs) from the United States, the U.K. and Germany.
- CFS symptoms during pregnancy improved in one-third, worsened in one-third and remained unchanged in one-third of study participants.
- A recent large study of prognosis concluded that the course of CFS waxes and wanes, but only about 10 percent of patients achieve complete remission.
- Central nervous system involvement in CFS is supported by predictable decreases in CRH, ACTH and cortisol; by elevated prolactin in response to serotonin stimulators; by growth hormone deficiency; and by brain imaging studies.
- While higher order skills are preserved, cognitive studies in CFS demonstrate deficits in complex information processing, processing speed, acquisition of new information and learning, or recall of complex material.
- A reduced blood volume (red blood cell mass) and prolonged acetylcholine-mediated vasodilation of the microcirculation occur frequently in CFS.
- Sleep is less efficient, sleep onset is delayed, and sleep study abnormalities (apnea, leg movement, restless legs and narcolepsy) occur in up to 50 percent of CFS cases.
- Therapy of sleep abnormalities is only modestly effective in improving CFS symptoms.
- Activated circulating lymphocytes are increased in CFS. Research in animals shows that such lymphocytes can cross the blood brain barrier to activate other lymphocytes and dendritic cells. This effect may persist for years.
- Activated microglia secrete proinflammatory cytokines and nitrous oxide, causing a chronic low-level injury.

- Several studies find higher rates of apoptosis (programmed cell death) in white blood cells in CFS.
- Inflammatory cytokines are elevated at the onset and over time in many patients infected with parvovirus B19. Persistent fatigue is best correlated with elevated gamma-interferon.
- PCR plus Southern blot demonstrated at least one species of mycoplasma in 179 of 261 study subjects with CFS, compared to 2 out of 36 healthy controls. *M. hominis* and *M. pneumonia* were most commonly identified.
- Nucleic acid gene expression techniques have demonstrated persistent deficiencies in oxidative phosphorylation, glycolysis and glucose metabolism in PWCs.
- Reduced levels of vitamin D have been found to cause muscle pain and other symptoms, and are seen in some patients with fibromyalgia.
- Endogenous levels of omega-3 fatty acids are reduced in chronic illness and may be associated with an increase in inflammatory mediators and reduced antiviral activity. Small trials suggest that replenishment of omega-3s may have value.

Epidemiology overview

Dr. William Reeves (chief of Viral Exanthems and Herpesvirus Branch, NCID, Centers for Disease Control and Prevention) provided an entertaining and comprehensive overview of CFS epidemiologic studies performed over the past several years.

Reeves noted that in the United States, the prevalence of CFS in two large population-based studies ranged from 235 per 100,000 (from 34,000 households with 90,000 individuals polled in Wichita, Kansas) to 422 per 100,000 (a study of 18,000 adult respondents in Chicago).

It's estimated that there are approximately 800,000 cases of CFS in the United States, and it appears that only 10-17 percent of these have actually been diagnosed by a physician or provider. Approximately 25 percent are unemployed or on disability.

A 2004 CDC study showed that the annual economic burden from CFS is estimated to be

\$9.1 billion, roughly equivalent to the entire annual profit margin of Wal-Mart. This figure only includes lost workplace and household productivity; it doesn't include health care costs. (In the United Kingdom it's estimated that the direct cost of medical care adds a burden of \$4 billion per year.)

Other data from the United States reveals:

- Two to five times more women have CFS than men.
- Adults have five times more risk than adolescents.
- Minorities are at higher risk.
- People in lower socioeconomic levels are at higher risk for CFS.
- About 80 percent of subjects report gradual onset.
- While there are no regional differences in prevalence, the prevalence is higher in rural than urban areas (for "CFS-like" cases).

Reeves described some problems with the current case definition for CFS and indicated that such problems are constantly being identified and worked out by the CDC. By way of example, he listed several instruments the CDC has recommended for measuring such features as overall function (SF-36), fatigue (MFI, CIS, Chalder Scale), psychiatric overlay (CIDI or SCID), cognition (CANTAB, Rozelle or Cognitive Function Index), sleep (Sleep Answer Questionnaire), pain (McGill Pain Score) and symptoms (the evolving CDC symptom inventory). Updates are posted on the CDC website (www.cdc.gov).

He reported that other goals of the CDC are to determine if CFS is a single illness; to define the natural history and clinical presentation of the disorder; to identify risk factors and diagnostic markers; and to devise both control and preventive strategies. "At this point," Reeves opined, "we know more about what CFS *is not* than what it *is*."

Fibromyalgia intensive

Dr. Daniel Clauw (chair, Department of Medicine/Rheumatology, University of Michigan) concluded the morning overviews with a review of current trends in FM. The 1990 American College of Rheumatology definition is being reexamined, he explained, as researchers view FM less as a discrete illness with focal



An impromptu panel moderated by Dr. William Reeves was convened at the conference to discuss the pros and cons of a proposed central research network for CFS. Panelists included Dr. Nancy Klimas, Dr. Tony Komaroff, Dr. Birgitta Evengard, Kim McCleary, Dr. Leonard Jason and Dr. Kenny De Meirleir.

areas of pain, and more as a continuum of illness with diffuse tenderness and associated somatic symptoms. It is also being recognized that psychological and behavioral factors play a negative role in some cases.

Tenderpoints may be less helpful than we once thought (studies indicate they correlate better with emotional distress than to disease severity), and they give the unfortunate impression that FM is mostly a muscle disorder, while most practitioners recognize that FM encompasses both rheumatic and multisystem symptoms.

Women are 1.8 times more likely to report widespread pain than men, but 10 times more likely to contract FM. The prevalence of FM is increased eight-fold in first-degree relatives according to Clauw, whereas the risk is only two- to four-fold for other rheumatic disorders such as rheumatoid arthritis and lupus, "making FM the most familial rheumatic disease." He feels that genetic markers of FM identified to date, however, are mostly related to comorbid psychiatric illness, not FM alone.

Pain amplification is clearly present in FM and attributed to both central and peripheral abnormalities, but cannot be explained by emotional or psychological factors. Persons with FM (PFs) perceive that a given pain is more severe than do healthy controls, and the threshold for other sensations (noise, heat and electrical stimulation, for example) is also reduced. The lower threshold for sensing pain is corroborated by functional MRI (fMRI) studies.

Depression has almost no role in pain processing, but “catastrophizing” or feeling “out of control” may exacerbate the perception of pain.

Increased levels of corticotropin-releasing hormone (CRH) are found in the cerebrospinal fluid of PFs, and the level correlates with pain levels.

Abnormal pain perception is not unique to FM, but is also seen in irritable bowel syndrome, temporomandibular dysfunction, muscle contraction headaches, chronic low back pain, vulvodynia and complex regional pain disorders, suggesting that there is some commonality among these. Two mechanisms offered for this are “wind-up” and the absence of DNIC (diffuse noxious inhibitory controls), both of which are being extensively studied.

FM therapy is commonly centered on managing pain. Three approaches to management include counseling/support, opioids and manipulating the antinociceptive (serotonin- and noradrenaline-related) pathways of the central nervous system. Clauw gave examples of several drugs that modulate pain by enhancing serotonin-enhancing, noradrenalin-enhancing or mixed pathways (see table below).

| DRUGS FOR FM PAIN | | |
|---|--|---------------------------|
| Serotonin-enhancing | Mixed | Noradrenalin-enhancing |
| citalopram fluvoxamine sertraline paroxetine fluoxetine | amitriptyline imipramine milnacipran | duloxetine venlafaxine |

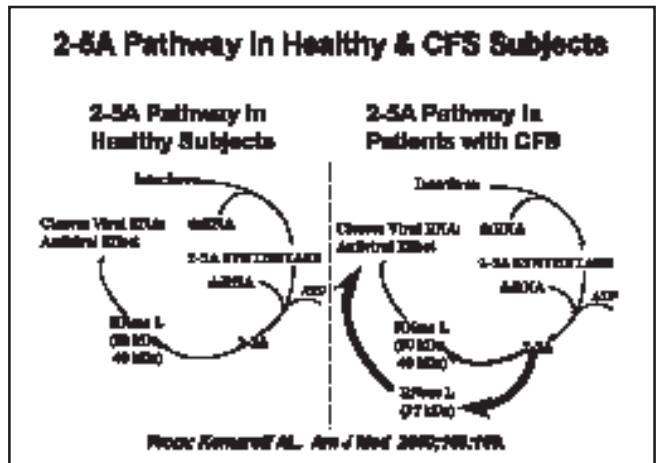
Papers and presentations

More than 30 papers were selected for presentation at this year’s research session, of which several were clearly outstanding. Following is a brief review of some of the major presentations.

Dysfunction of RNaseL pathway

Robert Suhadolnik, Ph.D., updated research he and colleagues have done on the 2,5-OAS RNaseL antiviral pathway. Even more studies in various patient populations confirm that this

antiviral enzymatic pathway is dysregulated in CFS, and a novel low molecular weight RNaseL is elevated in CFS but not in depression. The presence of low molecular weight RNaseL correlates with functional capacity, cognitive function and the number and activity of natural killer cells.



Elastase activity related to exercise capacity

Jo Nijs, Ph.D., of the Free University of Brussels, introduced attendees to the importance of elastase in persons with CFS. Previous studies have established that persistent activation of the 2,5-OAS pathway in CFS leads to elevated levels of RNaseL, which is cleaved in turn by capsain and elastase to a more biologically active form of low molecular weight RNaseL. Also, higher levels of RNaseL correlate with reduced exercise ability (Snell 2002).

Sixteen PWCs (no controls) underwent exercise stress testing in this study. Oxygen uptake at a respiratory quotient of 1.0 (RQ of 1.0 is about equivalent to the anaerobic threshold) was reduced compared to predicted norms. Increased levels of plasma elastase activity correlated with reduced oxygen uptake, but scores on a symptom inventory, MOS SF-36 scores, RNaseL, PKR and nitrous oxide levels did not. Elevated elastase levels could conceivably damage lung tissue and impair oxygen diffusion across alveoli in the lungs, possibly explaining decreased oxygen delivery to tissues in CFS.

Interferon-alpha connection to CFS?

Charles Raison, M.D., pointed out that

when interferon-alpha (plus ribavirin) is administered therapeutically to persons with a chronic hepatitis C viral infection, many subjects develop a CFS-like illness. Before treatment, 3 percent of patients met criteria for CFS, but during treatment 30 percent developed symptoms consistent with CFS.

Dubbo infection outcomes study

An interesting study from the rather isolated population of Dubbo, Australia, was described by James Jones, M.D., of the CDC. A prospective study of persons who contracted three well-characterized infectious illnesses (mononucleosis, Ross River Virus and Q fever) demonstrated that 10-15 percent of victims met CFS criteria at 6 months and 5-6 percent continued to meet criteria at 12 months after infection. Neither the premorbid psychiatric profile nor any biological marker predicted who would develop CFS.

STAT-1 proteins in CFS

STAT-1 proteins mediate the cell response to cytokines, particularly interferons. Konstance Knox, Ph.D., reported that in a recent study, 32 percent of CFS patients lacked this protein, whereas only 4 percent of healthy controls were deficient. Researchers speculate that this immunodeficiency in a subset of CFS patients may underlie the increased susceptibility to infections seen in some CFS patients.

Hypercoagulability in CFS

Harold Harrison, M.D., Ph.D., proposed that procoagulant genetic factors play a role in CFS and FM. His group studied tests of coagulability (such as fibrinogen and soluble fibrin monomer) and genes that control coagulability (such as protein C and protein S). Eighty-four percent of the subjects had at least one positive test, a prevalence three times greater than the general population, according to Harrison. The research group postulates that a subset of PWCs suffers with low-grade coagulation (“sludge”) in the microcirculation, which could explain many symptoms of CFS.

Complications of POTS

Julian Stewart, M.D., Ph.D., a pediatric cardiologist from New York Medical College, presented a straightforward but elegant study of circulation changes in young adults with postural orthostatic tachycardia syndrome (POTS). He described three subsets of patients (high-, low- and normal-flow POTS), all of whom demonstrated a marked decrease in thoracic blood volume on head-up tilt-table testing. Normal- and low-flow subjects also demonstrated pooling of blood in the splanchnic (abdominal) area during the same maneuver.

Stewart concluded that orthostatic intolerance can be produced by a number of mechanisms, among them low blood volume, autonomic problems and local abnormalities of blood flow and blood

pressure regulation, but not necessarily an autonomic dysfunction.

Cerebral blood flow in CFS

Cerebral blood flow is reduced in CFS patients, reports Kazuhiro Yoshiuchi, M.D., Ph.D., of the University of Tokyo. He used xenon computerized tomography scans of 25 patients and 7 healthy controls to demonstrate significantly reduced blood flow in the temporoparietal regions and the inferior right frontal cortex. While this has been reported by other groups, previous studies have been criticized for not considering the effect of depression on blood flow. Yoshiuchi stratified the sample by comorbid psychiatric diagnoses and found that these did not affect the results.

Serotonin transporters reduced in CFS

Hirohiko Kuratsune, M.D., of Osaka University School of Medicine used positron emission tomography (PET) to monitor serotonin transporters in the brains of 10 CFS patients and 10 healthy controls. He demonstrated a reduction in serotonin transporter molecules in various regions of the brain. In addition, the density of the 5-HT transporter of the dorsal anterior cingulate cortex correlated negatively with pain scores. Although depressed controls were not studied, previous studies have not shown evidence of similar deficiencies in depression. ■

Clinical Section

Saturday, October 9 - Sunday, October 10

By Charles W. Processing FM pain

Lapp, M.D.

Angela Lyden, M.S. (University of Michigan), and her group examined the response to two sensory experiences—somatic pain and exertion during exercise—in 27 FM patients and 39 healthy control subjects. Thermal pain, in the form of pressure applied to the thumbnail and thermal stimulation of the forearm, and the pain of exertion during graded exercise on a treadmill were tested. Thermal pain and the perceived pain of exertion correlated well, suggesting these two sensory experiences are potentially processed similarly in the brain.

Physiological responses to exercise

Anne Garcia-Quintana, M.D. (Hospital Valle D'Hebron and Delfos Medical Center in Barcelona), presented a study conducted in Spain comparing 50 people with CFS with 10 sedentary and 16 active young individuals using an arm ergometer and a bicycle ergometer. This confirmed previous studies showing that PWCs have a markedly reduced aerobic work capacity on bicycle ergometry, but demonstrated that they also have reduced upper body work capacity. Plasma lactate was also decreased in the more physically impaired. Study results may help PWCs understand why upper body activity is so exhausting.

Processing FM pain

José Alegre-Martin, Ph.D., provided demographic data, signs, symptoms and physical findings from 350 subjects from the CFS clinic at Delfos Medical Center in Barcelona. These Spanish patients were remarkably similar to other reported patient populations with respect to demographics, symptoms, orthostatic intolerance and reactive depression. Of special note: the onset of symptoms was gradual in 50 percent of their patients. While 10 percent of the patients improved, 54 percent reportedly worsened. In the United States CFS is usually described as nonprogressive.

Do support groups help?

Patients frequently ask their doctors whether or not it would be beneficial to join a support group. A recent study provides some insight into how to advise patients.

Fred Friedberg, Ph.D. (SUNY-Stony Brook), distributed a survey to 32 active members and 135 inactive (or dropout) members of a local support group. The support group included people with CFS (76%), FM (62%) and multiple chemical sensitivities (28%). Respondents rated the course of their illness since joining the group as better (52%), worse (29%) or unchanged (19%); severity scores in active members were significantly higher than in the inactive group. More than 80% of the full sample considered the support group helpful.

The most frequently cited reasons for attending were illness legitimization (68%), new information (66%) and feeling understood (62%). Lower endorsements were given to finding (35%) and dealing with (39%) physicians. The most common reasons for dropping out were inconvenient location (38%) or time (37%), negative talk (33%) and being too sick to attend (29%).

Occupational disability in CFS

Jo Nijs, Ph.D. (Free University of Brussels), presented a study that sought to establish valid assessments of disability in 27 PWCs using cardiopulmonary exercise testing (using a bicycle ergometer), a proprietary symptoms questionnaire and the SF-36. Half the patients were on disability. This study did *not* find a correlation between disability status and any other parameter. This was somewhat surprising because other groups have demonstrated the effectiveness of cardiopulmonary exercise testing (CPXT) in determining disability, and the United States Social Security Administration uses CPXT as one objective measure of impairment.

Ampligen trials

David Strayer of Hemispherx Biopharma

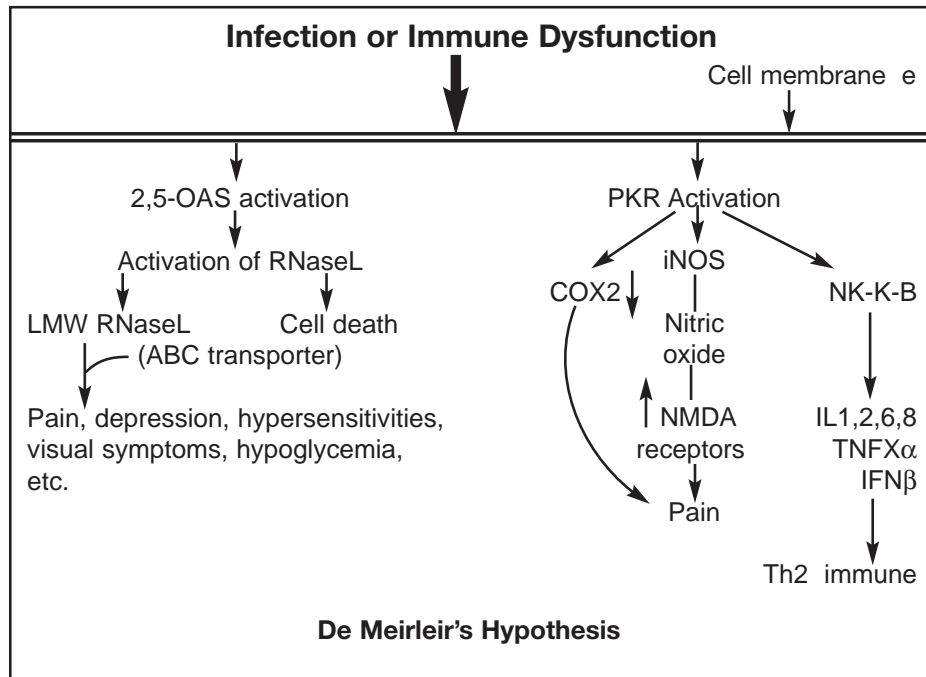
reported on a Phase III randomized, double-blind, placebo-controlled crossover study of 234 subjects treated with parenteral Ampligen (400 mg. twice weekly) for 40 weeks. The dropout rate and serious adverse events were slightly increased in the treatment group compared to placebo, but the differences were not statistically significant ($p > 0.10$).

Exercise duration in the treatment group was 16.1 percent greater than placebo (in completers) and 15.2 percent greater than placebo in all participants (intent to treat analysis, $p < 0.05$). These increases in exercise duration were more than twice the minimum considered medically significant (6.5 percent). Maximum oxygen utilization was markedly improved in treated (6.07) versus placebo (0.58) subjects.

There were no significant adverse events or significant abnormalities in laboratory parameters. Ampligen treatment in this debilitated population of CFS patients resulted in a medically and statistically significant improvement in the primary end point—exercise treadmill duration—compared to placebo. Ampligen may be the first drug to demonstrate safety and effectiveness in the treatment of CFS.

Managing CFS as an immuno-vigilance disorder

Kenny De Meirleir, M.D., Ph.D. (Vrije Universiteit Brussels), challenged the conventional view of CFS as a disorder that has no known pathophysiology. He stated



confidently that enough is known about the disorder to treat it in a scientific manner. He used two cellular antiviral systems, oligoadenyl synthetase (OAS) and phosphokinase (PKR), as examples. In the OAS system, infection and mild immune dysfunction activate OAS, which then produces an enzyme RNaseL, which leads to cell death and, in CFS, to the production of a novel low molecular weight RNaseL.

Truncated or low molecular weight RNaseL can cause multiple symptoms (increased pain, depression, hypersensitivities, visual symptoms and hypoglycemia) via the ABC transporter system. De Meirleir also stated that activated OAS can suppress the thyroid even though thyroid function tests appear normal.

Activation of PKR pathways, on the other hand, leads

to activation of NF-kappa-B, the iNOS gene and cyclooxygenase (COX2) pathways. These changes switch the immune system to a Th2 state, suppress the hypothalamic-pituitary-adrenal axis and cause both vasoconstriction and platelet aggregation.

De Meirleir, therefore, sees chronic fatigue syndrome as a Th2 immune disorder with activated PKR, activated OAS and an elevated RNaseL. He believes that effective therapeutic interventions might include restoring immune competence, treating hormonal changes and treating infections and allergies. He provided two case studies of PWCs in whom triggers were identified and focused therapy produced remarkable improvement.

Lyme disease and CFS

Dr. Stanley Schwartz, who practices at the Warren Clinic

in Tulsa, Oklahoma, is an infectious disease specialist who tackled the difficult question of whether chronic Lyme disease and CFS are the same illness. This question arises because people with previous Lyme infection sometimes develop CFS-like symptoms. A minority of physicians attributes such symptoms to persistent *borreliosis* and recommends long-term antibiotic therapy. The majority concludes that short-term therapy is sufficient to destroy the Lyme organism.

If symptoms last longer than six months after a tick bite, is it chronic Lyme disease (LD) or CFS? To answer this question, Schwartz reviewed the extant literature on chronic LD, but he concluded that it's not clear if fatigue after LD is a form of CFS, is an unresolved infection, or is due to an immune abnormality. Antibiotic therapy has not conclusively been shown effective in randomized controlled trials of chronic LD.

Schwartz made the important point that Lyme disease is a clinical diagnosis, and that laboratory tests for LD may be unreliable in patients who don't have a reliable history of clinical Lyme disease. Accepted tests include the ELISA, Western blot, skin biopsy or synovial PCR. There are many other investigational tests, but he believes these are unreliable for a diagnosis.

CFS case definitions

People with CFS (PWCs) are clearly a heterogeneous group with diverse signs and symptoms. Just as there are many causes for cancer, it seems that there are various triggers and forms of CFS. This heterogeneity makes CFS difficult to define precisely. Over the years several clinical case definitions have been suggested, but they clearly select slightly different populations. As a result there is a lack of consistency in related studies using different criteria.

Leonard Jason, Ph.D. (DePaul University), and Nancy Klimas, M.D. (University of Miami), took a look at various case definitions in their presentation. Jason points out that CFS samples using different definitions invariably have different critical symptoms (e.g., many emphasize fatigue, but others emphasize a lack of energy); use different case ascertainment methods; and

select different degrees of psychiatric morbidity, sociodemographic types and biologic groups. Even the course of disease and the rate of disability may be different between definitions. Jason argues that a case definition should be derived empirically and specify certain subtypes in order to improve reliability, specificity and sensitivity.

Jason points out that the 1994 Fukuda criteria are internationally accepted and widely used in current research. These criteria were developed by a consensus group assembled by the CDC. In addition, the CDC hosts meetings periodically to update and revise these criteria, which are referenced on the CDC website.

Subtyping patients was recommended by the authors of the Fukuda criteria (Fukuda, et al. *Annals of Internal Medicine*, 1994), but they provided no specific recommendations. Subtyping could further define the patient population for research purposes and might define appropriate groups for targeted therapies. Klimas warned, however, about overgeneralization. Generalizing from subgroup data requires follow-up trials to determine if the results can be extrapolated to the larger population.

Klimas suggested a number of ways to subtype patients, including:

- Symptoms/history subgrouping (duration, age at onset, severity, gender, ethnicity, socioeconomic class, functional status, etc.)
- Cognitive-predominant versus pain-predominant
- Based on onset—acute versus slow
- Based on systems involved (immune, autonomic or neuroendocrine)
- Based on gene expression patterns
- Based on psychiatric diagnoses (depressed, anxious, compulsive, neurotic, etc.)
- Based on physical findings (such as tenderpoints, a positive Romberg or hyperextensible joints)
- Based on objective measures
 - Low cortisol (neuroendocrine grouping)
 - Abnormal tilt test (autonomic or orthostatically intolerant group)
 - Activation or cell markers, cytokine elevation (immune group)
 - Abnormal PASAT or other cognitive study (neurocognitive group)

Case definitions and criteria will, no doubt,

CFS CASE DEFINITIONS

| DEFINITION | SUBSTANCE | COMMENTS |
|--|---|---|
| Ramsey Definition (1981) | Fatigue occurs after minimal exertion and there may be a delay. Symptoms of circulatory impairment. Symptoms of CNS impairment. At least 6 months duration. | The first true case definition. |
| London Criteria (Goudsmit, 1992) | Exercise-induced fatigue. Neurological disturbance. Fluctuation of symptoms. Ongoing symptoms for > 6 months. | Selects more symptomatic patients than 1994 Fukuda criteria (below). |
| Australian Case Definition | Exercise-induced fatigue, disrupting daily activities, of > 6 months duration. Neuropsychiatric dysfunction and new short-term memory loss. No alternative diagnoses. | Postexertional malaise and neurocognitive problems are the major symptoms, not fatigue. |
| 1988 U.S. Criteria (Holmes, et al) | Chronic unexplained fatigue. No other plausible explanation. At least 8 of 11 symptoms or 2 physical findings and 4 symptoms. | Physical findings were difficult to document, and symptoms were poorly defined. |
| 1994 International Criteria (Fukuda, et al.) | Chronic unexplained fatigue that is not lifelong but at least 6 months duration. No other plausible explanation. At least 4 of 8 symptoms (myalgias, arthralgias, new headache, non-exudative pharyngitis, lymphadenopathy, cognitive dysfunction, post-exertional malaise, unrefreshing sleep) | Internationally accepted and used. Selects fewer symptoms than 1988 criteria, but more impaired subjects (based on MOS SF-36). Exclusions are specified. Requires thorough medical history and mental status exam. Basic lab panel and assessment instruments suggested. |
| Canadian Consensus Definition (2004) | Marked fatigue that reduces activity (required). Postexertional malaise (required). Nonrestorative sleep or disturbance (or acute onset required if not present). At least 2 neurocognitive symptoms. At least 2 symptoms from autonomic, neuroendocrine or immune categories. | Selects reduced psychiatric morbidity compared to 1994 Fukuda criteria, but more severe physical impairment, fatigue or weakness, and neurocognitive symptoms. |

When the three case definitions were used with a group of chronically fatigued patients, the Holmes criteria selected the fewest subjects, the Fukuda selected the highest number, and the Canadian fell in between.

continue to evolve as researchers and clinicians learn more about CFS. In the meantime, the lack of consistency impacts both research and patient care. ■

Clinical Workshops

By **Charles W. Lapp, M.D.**

Three clinically relevant mini-seminars were presented at the Madison conference. While it's difficult to capture these workshops briefly, the substance is summarized below.

1. Cognitive behavioral therapy

Cognitive behavioral therapy (CBT) was initially brought to the attention of clinicians by British psychologists who subscribe to the idea that somatic symptoms in CFS and FM are perpetuated by errant illness beliefs and maladaptive coping. Their theory suggests that people with CFS or FM have certain abnormal cognitions and behaviors that perpetuate their symptoms and impairments. More recently, CBT has been applied to a number of supportive interventions ranging from the British approach to supportive counseling, education and even nonpharmacologic therapies.

In all the confusion, CBT has become an all-encompassing, "wastebasket" term. To bring order to the chaos, I organized a mini-symposium on CBT featuring speakers with diverse perspectives. Their combined talents provide a wonderful framework for providers, counselors and patients.

Dr. Fred Friedberg

Fred Friedberg, Ph.D. (SUNY-Stony Brook), is an early CFS pioneer who has written widely and been extremely active in regional support groups. His experience with CBT has been positive, but he wonders, "Does CBT improve coping, or does it actually improve the patient?" The answer is unknown, of course, but Friedberg suggests that CBT does help patients take back control over their life and health. He referred to a 1997 paper in which Rey concluded that if a patient has little sense of control, then limiting activity and stress actually increases impairment because the patient feels further constrained or victimized. If the patient is given a strong sense of control, however, limiting activity and stress leads to improvement. Lack of control may come from severe illness, lack of support or poor coping,

but achieving control for the patient is fruitful.

Friedberg encourages patients to balance activity with rest and requires them to sustain appropriate lifestyle changes. Specific therapies include relaxation techniques, sleep hygiene, anger management, pleasant mood induction, pacing and graded activity.

Dr. Elke Van Hoof

Elke Van Hoof, Ph.D. (Free University of Brussels), provides one-on-one counseling to patients at a well-known CFS clinic in Belgium. Van Hoof feels that CBT should define the patient's cognitions and modify them to reduce symptoms and improve quality of life. The Brussels model utilizes a team approach, which places a priority on medical therapy first, then behavioral therapy that may include CBT and psychiatric counseling.

Van Hoof uses a "phase approach" developed by Patricia Fennell that places patients in one of four phase groups. In Phase I (crisis) the patient is usually functioning poorly, chaotic, emotional and "out of control." In this phase Van Hoof and her team explain the biological model of CFS and introduce therapeutic strategies. Social assistants help obtain state and financial support including disability, if warranted. A social framework is established by asking a partner, friend or family members to also attend sessions. The purpose of Phase I is to return control to the patient, as well as to provide illness insight and information.

Phase II (stabilization) increases the patient's adherence to therapy, motivates the caregiver to be a coach, increases self-efficacy, addresses victimization and life events, and introduces pacing and limit setting.

Phase III (resolution) is the time to identify perpetuating factors, challenge negative thoughts and set realistic goals.

Finally, Phase IV (integration) attempts to reintegrate the patient with work or school, while avoiding relapse.

Dr. Mary-Catherine Segota

Mary-Catherine Segota, Ph.D., introduced

us to a 12-week group therapy program called Stress Management and Relaxation Training, or SMART, developed at the University of Miami. Weekly two-hour group sessions consist of 90 minutes of didactic learning and cognitive restructuring and 30 minutes of relaxation and guided imagery. Elements of instruction include education (using the biopsychosocial model), cognitive restructuring, adaptive coping skill training, quality of life enhancement and graded exercise.

Session 1 deals entirely with stress management strategies and how to identify and change negative thought patterns.

Sessions 2-5 teach that thoughts and emotions affect how one feels, and that the individual has control over these. The sessions also deal with cognitive distortions such as all-or-nothing thinking, overgeneralization, magnification and “should” statements.

Sessions 6-8 are devoted to resolving interpersonal difficulties, teaching communication, assertiveness and listening skills, as well as conflict resolution and anger management.

Sessions 9-12 focus on helping participants develop more realistic expectations, reprioritize different aspects of their lives and increase successful experiences.

2. Exercise in people with CFS and FM

This workshop highlighted three slightly different

approaches to exercise, all based on the understanding that people with CFS or FM suffer exercise intolerance and postexertional malaise unless they stay within prescribed limits. Two groups (Hunter-Hopkins Center and Workwell) suggested that “the limit” is probably a person’s anaerobic threshold (AT)—that time during exertion when the heart and lungs can no longer provide adequate oxygen to muscles, and muscle metabolism changes from aerobic to anaerobic. It’s well known that the AT occurs unusually early in people with CFS and FM.

Dr. Charles W. Lapp

Charles Lapp, M.D. (Hunter-Hopkins Center), explained the basis for the exercise prescription by demonstrating how cardiopulmonary exercise testing is performed and how the AT is determined in the laboratory. He then described one approach used in his Charlotte clinic, low-level interval activity, which presumes that flares and relapses occur if patients exert beyond the anaerobic threshold. If the AT is determined to occur at four and a half minutes, for example, then the patient is advised to exert no more than four to four and a half minutes before stopping to take a five-minute rest. Depending on how the patient feels, he or she may perform one repetition on a “bad day” or several on a “good day.”

Walking, bicycling and swimming are the preferred

forms of exercise, but interval activity applies to all daily activities of exertion, including cleaning, vacuuming, carrying groceries and gardening. Lapp and others have validated this technique in debilitated PWCs who were able to walk on a treadmill for 10 repetitions of three minutes each without triggering a flare (*Physical Therapy*, 1999).

Staci Stevens and Dr. Christopher Snell

Staci Stevens, M.A., is CEO of Workwell Foundation and an exercise physiologist who has designed rehabilitation programs for PWCs for more than 15 years. Chris Snell, Ph.D., is an exercise physiologist and professor in the Sports Sciences Department at the University of the Pacific. They believe PWCs fall into two basic types, roller coasters or energy avoiders. The roller coasters tend to overexert then collapse, so the goal is to slow them down to a moderate pace. The energy avoiders tend to shun exercise, so the goal is to find activities they can participate in safely, without triggering a flare-up.

The group has published widely on the use of cardiopulmonary exercise testing for impairment (disability), and their work confirms other studies showing there is “oxidative impairment” in CFS and FM. In other words, the AT occurs prematurely in most subjects, and when a patient exceeds the AT, he or she incurs an “oxygen debt.”



Dr. Chuck Lapp



Dr. Chris Snell and Staci Stevens

Such an oxygen deficit leads to fatigue and other symptoms, and for some patients even daily activities like bathing or dressing may be limited. Stevens and Snell point out that oxygen debt has to be paid back by resting.

The Workwell team defines exercise in terms of 30-second intervals. They emphasize that the initial goal is to improve functional movement, then train the short-term energy system, then improve range of motion and functional strength. Their program starts with stretching and strengthening with no resistance; then resistance training (using very light weights or elastic bands); then interval training; then a maintenance program.

Janice H. Hoffman

Janice Hoffman is a clinical exercise specialist and research team member at the Oregon Health & Science University (OHSU) in Portland. She has conducted several studies of exercise with FM patients for the OHSU team, which includes Drs. Kim Dupree Jones, Sharon Clark and Robert Bennett. Hoffman described the approach that is employed at the OHSU fibromyalgia clinic in Portland.

The OHSU program follows a four-step progression. The first step—body alignment—addresses abnormal pain postures, most notably the tightened-chest, high-shouldered, head-forward posture seen in most people with FM, especially when they are tired or in flare. Subjects are advised to avoid prolonged sitting, which exacerbates such postures and increases fibropain.

Standard deep (abdominal) breathing and progressive relaxation techniques are taught next. Hoffman points out that most people with CFS and FM already have tense muscles, so relaxation techniques that require first tensing the muscles and then relaxing are avoided.

The third step addresses flexibility, which is improved with a number of prescribed stretches. Hoffman points out that these stretches should be slow, static and gentle (rather than rhythmic or pumping) and should last less than 10 seconds. Stretches are specifi-

cally directed at the neck and shoulder, but also aim to stretch the hip-flexors, quadriceps and hamstrings in the upper leg.

Resistance exercises are added next to build core strength, then all the major muscle groups. These are prescribed a maximum of twice weekly, and the left and right sides are alternated during repetitions to rest one side while the other is being exerted.

Unlike the previous two groups, the OHSU group uses heart rate rather than anaerobic threshold to prescribe endurance exercises. They limit exercise duration to 20-25 minutes, discourage highly repetitive movements and encourage patients to maintain a heart rate between 40-70 percent of their calculated maximum heart rate. Hoffman says a good benchmark for staying in a low to moderate aerobic zone is to be able to talk, but not sing.

3. Dysautonomia and orthostatic intolerance in CFS and FM

Dr. Lapp moderated a mini-seminar on dysautonomia and orthostatic intolerance (OI), which included two papers on recent investigational therapies.

Dr. Julian Stewart

Julian Stewart, M.D., is professor of pediatrics and physiology at New York Medical College. He has established a Center for Hypotension-Related Disease that treats young people ranging from children to young adults.

Stewart defines orthostatic intolerance (OI) as the inability to tolerate the upright position. OI may be associated with a number of symptoms including fatigue, nausea, headache, light-headedness, abdominal pain, sweating, tremor, weakness, anxiety and depressed feelings. He described how tilt-table testing is used to distinguish the various forms of OI, namely orthostatic hypotension, postural orthostatic tachycardia syndrome (POTS) and neurally mediated hypotension (NMH).

When a person stands, gravity pulls a pint or so of blood into the lower extremities, reducing blood pressure in the upper body and brain. The heart and brain blood flow are initially not affected, and blood pressure is typically maintained for at least the short term. This normally

produces an increase in heart rate of 10-15 beats per minute. In orthostatic hypotension the heart rate usually increases slightly, but blood pressure falls.

POTS is defined as an increase in heart rate of 30 or more beats per minute within five minutes of upright tilting. Stewart presented an earlier paper espousing that POTS may not be an autonomic disorder, but instead may be due to decreased blood volume in the upper body or thorax.

NMH (also known as simple faint, vasovagal faint and neurocardiogenic syncope) is characterized by an initial increase in heart rate and blood pressure, followed by a rapid decline in both (associated with disorientation, sweating and eventual fainting). Fainting can trigger a prolonged flare of CFS or FM.

In his role as moderator, Lapp emphasized a number of points about tilt-table testing in CFS and FM:

- Tilt-table testing must be performed properly (after a prolonged supine period, in a dark quiet room, in the absence of medications and other causes for orthostatic intolerance).
- Passive studies (using no stimulant medications) are preferred by most.
- Terminating the tilt-table study before frank syncope can prevent prolonged flares.
- Orthostatic hypotension, when present, occurs within seconds to minutes of standing upright and may occur in anyone. It's not typical of CFS or FM.
- Orthostatic intolerance is delayed by many minutes in PWCs, whereas it occurs promptly in other disorders (such as Addison's disease, diabetic neuropathy or Shy-Drager Syndrome).

Dr. David Bell

David Bell, M.D., is a true pioneer in the field of chronic fatigue syndrome and the pre-eminent expert on pediatric CFS. In the past few years Bell worked with the late David Streeten to study orthostatic intolerance and blood volume in PWCs. For this conference, Bell described his experience with RBC mass and ADH in PWCs.

Bell randomly measured the red blood cell mass (RBCV) and plasma volume (PV) using the Cr51 technique in 19 PWCs. Sixteen of these had significantly reduced RBC mass

compared to predicted control values. Ten had reduced plasma volume, but this was not statistically significant and tended to vary based on the level of the patient's hydration at test time. In another study of 72 PWCs, 73 percent had a RBCV less than 23 ml/kg (low), while 44 percent had a RBCV less than 20 ml/kg (very low).

Bell then recalled a paper by Bakheit (1993) that described low antidiuretic hormone levels in 9 patients with CFS. Bakheit suggested that low ADH would lead to functional dehydration and that volume expansion might help such patients. Bell initiated a pilot study of 17 PWCs, who were given intravenous fluids (normal saline) daily for at least three months. The outcome of this experiment was that 5 patients (30 percent) had a slight response, 10 had a good response (60 percent) and 2 quit the study early. While IV fluids may help, it is neither practical nor safe to use this therapy widely. Six patients developed infections from placement of the IV PICC lines.

Dr. Barry Hurwitz

Barry Hurwitz, Ph.D., is a professor at the University of Miami and at the Behavioral Medicine Research Center/VA Medical Center in Miami. Hurwitz is the principal investigator, with Nancy Klimas, on an NIH-sponsored, five-year study of red blood cell mass and the autonomic nervous system in CFS.

In this "Procrit study," (double-blinded, controlled, crossover), PWCs with documented low RBC volume are treated with either epoetin (Procrit) or placebo, while PWCs with normal RBC volume are treated with placebo only. Data collected so far shows that 60 percent of females and 15 percent of males have a substantial reduction in their red blood cell volumes.

The Procrit study isn't completed, so Hurwitz has no basis for predicting whether epoetin will actually help PWCs. He and Klimas report that some subjects have shown an increase in red blood cells and have required special management to maintain the hematocrit in a safe range. There is a sense that treatment has improved symptomology in some patients, but only time will tell. ■



27 N. Wacker Drive #416
Chicago, IL 60606

E-mail: Admin@aacfs.org
Website: www.aacfs.org

Phone: 847-258-7248
Fax: 847-748-8288

MEMBERSHIP APPLICATION

Membership (check all that apply):

- New member Renewing member

For professionals (clinicians, researchers, therapists, disability specialists at doctoral level):

- 2 years, \$150 1 year, \$100 lifetime, \$1,000

For associate members, nonvoting (students, office staff, ARNP, RN at the nondoctoral level):

- 2 years, \$75 1 year, \$50

For individual supporting members, nonvoting (patients, general public, etc.):

- 1 year, \$40

For support group sponsors: \$200 suggested (based on ability to pay)

For individual or corporate sponsors:

- bronze, \$500 silver, \$1,000 gold, \$2,500
 platinum, \$5,000

Membership includes the AACFS newsletter, reduced conference registration fees, discounted AACFS materials and listing in directory of CFS professionals

- Please include my name in the planned directory of AACFS members who treat or assist CFS patients

Contact information:

Prefix (Ms., Dr., etc.) _____ Academic degrees _____

Name _____

Address _____

City _____ State/Province _____

ZIP _____ Country _____

Phone _____ Fax _____

E-mail _____

Occupation _____

Organization _____

Total amount remitted:

- Check (please make check or money order payable in U.S. funds to AACFS and mail to the address above)

- VISA MasterCard American Express (please mail to address above or fax to 847-748-8288)

Card number _____ Exp. date _____

Cardholder name _____

Cardholder signature _____

THE CFIDS ASSOCIATION OF AMERICA

PO Box 220398
Charlotte, NC 28222-0398
Phone: 704-365-2343
Fax: 704-365-9755
Website: www.cfids.org

Nonprofit
Organization
U.S. Postage
PAID
Richmond, VA
Permit 930

Forwarding and Return Postage Guaranteed
Address Service Requested