AFSA The American Fibromyalgia Syndrome Association, Inc.

UPDATE

Organizational News and Activities

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IN THIS ISSUE ...

MISSION:

To encourage scientific research toward finding the cause of and cure for fibromyalgia syndrome (FMS) as well as to promote public awareness and understanding of this condition.

To support educational, scientific and charitable activities undertaken exclusively in connection with FMS and related disorders.

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Three More Projects Funded!

Since our last *Update*, three very diverse projects have been funded by AFSA—we will summarize them in this issue! One study expands upon contributing genetic factors in fibromyalgia syndrome (FMS), while another is guaranteed to produce new developments in the field by providing much-needed brain and spinal cord tissue. Finally, one project focuses on a symptom that has not received the attention is deserves: SLEEP. Although AFSA has been somewhat "quiet" during the past two years (i.e., sending out *Updates* infrequently), we continue to work behind the scenes to fund promising studies with your generous contributions.

Focusing on Sleep Research

Sleep studies in FMS are difficult to find, yet disturbed sleep is a major contributor to one's symptoms. In fact, some researchers feel that the sleep disorder in FMS may actually cause this condition. Even patients with FMS firmly believe that their terrible quality of sleep contributes to how they feel. So why is it that almost all research in the field of FMS has focused on the symptom of pain, with so little attention given to sleep? In part, the answer has to do with how easy it is to measure pain through a tender point exam versus the expensive and entailed assessment of sleep with an overnight study in a lab. In addition, where would a sleep researcher go for seed money to conduct a study on FMS?

Potential researchers could come to AFSA with their sleep-related proposals, but a quick review of the many pain-related projects funded by AFSA might dissuade them from applying. As for the National Institutes of Health (NIH), it is hard to get a study funded by the government without preliminary data ... which is where AFSA comes in handy to jump-start investigators so that they are more likely to succeed at the NIH level.

In 2007, AFSA will turn up the heat on funding sleep-related research in FMS patients. We will set aside $250,000 for five (5) individual awards to clearly establish that AFSA is interested in receiving applications to study sleep. However, unless we have several top quality sleep researchers on our Medical Advisory Committee (MAC), potential applicants will be hesitant to spend time submitting their proposals. This is why sleep researchers are being added to the MAC. Sleep experts, **Jed Black, M.D.**, of Stanford University in California, and **Avram Gold, M.D.**, of Stony Brook University in New York, have already volunteered to be on AFSA's MAC.

During the next two to three months, AFSA will generate a list of research-funding priorities for FMS in the area of sleep. Then we will publicize our new funding initiative to the members of the sleep research community in hopes that we will be able to entice experienced investigators to enter the field of FMS. As the results of the awarded studies become published in the medical journals, more researchers will begin to think about FMS in terms of sleep, and AFSA-funded sleep researchers will begin to get their feet in the door at the NIH. It will take a few years for progress to be visible, but this is the same process AFSA used to jump-start pain-related research in FMS years ago (except we started with a much smaller sum of money).

END

Establishing a Fibromyalgia Tissue Donation Program for Studying Human Chronic Pain States

Principal Investigator: ***Dianne Lorton, Ph.D.***
Sun Health Research Institute, Sun City, AZ
Award Amount: $58,750

Effective treatments for FMS are needed, but this requires knowledge of what is happening in the cells of the central nervous system and other body tissues that are contributing to the symptoms. The purpose of this study is to enroll FMS patients into a post-mortem tissue donation program at Sun Health Research Institute (SHRI, a nonprofit research foundation), in which brain, spinal cord and other tissues/fluids will be collected.

"The SHRI tissue bank is world-renown for its quality of post-mortem tissue," says Lorton. "Post-mortem times average 2.5 hours, making it possible to use the collected tissue for research that is not possible with tissue from other banks (e.g., the quick collection time produces tissues that closely resemble how the cells functioned when the person was alive). Tissue collected from Alzheimer's and Parkinson's patients at SHRI are sent to researchers all over the world. Now it will be possible to extend this tissue bank to facilitate research on FMS."

These valuable tissues will be made available to scientists who submit top quality proposals to study FMS, which will rapidly expand our knowledge about this condition. Tissues will also be used to complete an already approved and funded project by AFSA (*Translation from Animals to Humans: Are Chronic Pain States in Humans Associated with Glial Activation in Spinal Cord and/or Brain?*).

The principal investigators of the above study are **Linda Watkins, Ph.D.**, of the University of Colorado at Boulder, and **Dianne Lorton, Ph.D.**, of SHRI. A full description of this project was provided in the May 2005 *AFSA Update* and can also be read online at **www.afsafund.org**. Glial cells amplify pain by releasing pro-inflammatory cytokines. Recent studies indicate that glia within pain-processing areas of the brain and spinal cord are critical to the maintenance of pathological pain, and animal studies show total pain remission with suppressed glial activity. It is unknown whether the glia are activated in FMS, but it is a strong likelihood given the studies showing elevated levels of pro-inflammatory cytokines in the blood.

This uncertainty about the involvement of glia in FMS sets it apart from low back pain, nerve damage pain, and other pain syndromes in which a rat model with glia activation has been demonstrated. In fact, for all of these pain syndromes, the rat models prove glial activation is key ... but FMS does not even have a rat model. While it is rather easy to interest pharmaceutical companies in targeting glia for pain syndromes where the glia are known to be involved, it has proven impossible to interest them in such clinical trials for FMS.

The purpose of this related study by Watkins and Lorton is to look for evidence of glial activation in the brain and spinal cord tissues of FMS patients collected shortly after death (e.g., from this tissue donor program). Comparisons will be made with other chronic pain syndromes and healthy control subjects. If glial activation is found, it would provide a strong argument for testing drugs that target glial activation as a solution for FMS pain.

The FMS tissue donation program is expected to recruit 70 FMS patients during its first year and 20-30 more each year thereafter. "SHRI has already enrolled 20 FMS patients thus far," says Lorton, "and are working through community education talks, local newspaper articles, SHRI facility tours, and outreach to physicians to increase enrollment." To ensure that all patients enrolled clearly have FMS and not a condition that may mimic it, their diagnoses must be independently confirmed by two experienced physicians. Also, enrolled patients will continue to be followed by SHRI's physicians on an annual basis to document any changes in their health status.

The establishment of a tissue donor program for FMS will accelerate knowledge about this condition and streamline the speed at which effective therapies can be developed. Lorton and SHRI are using their experience and resources to work with AFSA to develop an FMS registry to expedite research in this field. The project award is for a two-year period and was essential for demonstrating to the NIH that such a tissue bank for FMS could be successfully established.

Lorton submitted a grant application to the NIH's National Institute of Arthritis and Muculoskeletal and Skin Disease for the continuance and, hopefully, the expansion of this tissue donor bank. "Just recently," says Lorton, "SHRI's application was approved and awarded approximately $1.4 million over a four year period to further support the costly endeavor of developing an FMS tissue bank and to provide additional funding for Dr. Watkins' ground-breaking pain research."

END

Alterations in COMT Gene Contribute to Pain Susceptibility in FMS
Part 2- Comparison of large patient/control population in Mexico Versus Spain

Principal Investigator: ***Manuel Martinez-Lavin, M.D.***
National Institute of Cardiology in Mexico City
Award Amount: $16,800

Catechol-O-methyl-transferase (COMT) is an enzyme that breaks down catecholamines (a class of neurotransmitters): dopamine, norepinephrine and epinephrine. These transmitters are involved in the regulation of the sympathetic nervous system. Many studies have shown that the sympathetic system is dominant (hyperactive) in people with FMS, while the parasympathetic branch is not as active as it needs to be to aid with sleep and digestion.

Substitution of one amino acid for another, and other structural glitches on the COMT gene, can alter the speed at which the enzyme breaks down catecholamines. For example, if the amino acid valine is substituted for methionine in a specific region, then the COMT enzyme becomes "lazy" and degrades the catecholamines three to four times slower than normal (causing the catecholamines to accumulate). This sluggishness in the enzyme's action not only alters the way the sympathetic system works, *it also leads to a lower pain threshold* (i.e., greater pain sensitivity because excessive catecholamines interferes with the body's production of pain-relieving opioids). However, there are many other potential anomalies in the gene that controls the COMT enzyme, making the genetic evaluations more complex.

In the initial study conducted by Martinez-Lavin (Part 1), he evaluated 40 FMS patients and compared them to 40 age-matched controls (all women to minimize variations). He found that FMS patients tend to have a COMT gene variation associated with increased pain susceptibility.

"These preliminary results suggest that an altered COMT gene predetermines the autonomic dysfunction in a subgroup of FMS patients," says Martinez-Lavin. "It also provides gene-related support for the concept that FMS is a sympathetically maintained pain syndrome." In other words, the malfunctioning sympathetic system could be responsible for the symptoms in a subgroup of patients with the COMT gene alterations.

In order to uncover more genetic variations and differences between FMS patients and healthy controls, one must look at a larger group of people. In Part 2 of the project, Martinez-Lavin will be evaluating an additional 120 FMS patients and 120 healthy controls to add to his existing genetic data. In the end, he plans to have 80 patients and 80 controls from Mexico, and a parallel patient/control group residing in Spain. He is joining forces with another investigator, **Ferran García-Fructuoso, M.D.**, of Spain, who has collected DNA from a well-selected Spanish population. Looking at the genetic background of two different populations will undoubtedly strengthen the study. It will determine if the purported COMT gene abnormalities are similar in two different geographic areas.

"We want to add an important piece to the fibromyalgia jigsaw puzzle," say Martinez-Lavin. "The most consistent abnormalities found so far in fibromyalgia are the electrocardiographic changes of ongoing sympathetic dominance (the chart recording should show repeating fluctuations between sympathetic and parasympathetic control, but a sympathetic dominant signal has been reported by multiple researchers). If we find that a subgroup of patients have a genetic predisposition for this sympathetic dominance, it may explain why fibromyalgia *runs* in some families. The genetic alteration may possibly identify people at risk of developing the illness. If we identify early on people that do not degrade catecholamines properly, and at the same time are hypersensitive to pain perception, it would be possible to take preventive interventions."

According to Martinez-Lavin, Part 2 of his project is expected to be finished by mid-2007. **END**

CFS - Role of Sleep Disturbance and Exercise on Symptoms and Cytokine Production

Principal Investigator: ***Benjamin Natelson, M.D.***
University of Medicine and Dentistry of New Jersey, Newark
Award Amount: $35,100
(AFSA Awarded a Tag-on Project to this NIH-funded Study)

Natelson's ambitious NIH-funded project involves studying the sleep of patients during three nights in a sleep lab. The goal is to measure the impact of disturbed sleep and an exercise regimen on the next-day symptoms for CFS patients and their production of cytokines. Roughly 20% of CFS patients have measurable signs of obvious disturbed sleep (such as sleep apnea and restless legs syndrome), which means that the majority do not have a well-defined sleep disorder. Natelson excludes patients with these sleep disorders, leaving him with patients having sleep complaints that have no medical explanation. Then he divides his study group of CFS patients (many of whom overlap with FMS) into two different groups based on the results of their formal sleep study: those with disturbed sleep and many awakenings and those without disturbed sleep. For comparison, he will use an age-matched control group of women who do not have any symptoms of CFS (all CFS patients will be female because cytokine levels are higher in women and it is important to minimize variability in the data).

One hypothesis about the cause of CFS (and FMS) is that immune dysfunction leads to poor sleep, and that this immunological malfunction is linked to abnormal production of cytokines. Although cytokines have been studied in both CFS and FMS patients, no firm data exists to support the immunological ties between cytokines and sleep disruption or daytime fatigue in these patients. Cytokines are produced by the immune system and are suspected to be the neuro-immune link in CFS/FMS because the glial cells that secrete these substances reside within the central nervous system. Natelson suspects that cytokines are responsible for causing the sleep disorder in some CFS patients, and not the other way around. Due to the fact that he will be evaluating CFS patients with and without disturbed sleep, he hopes to be able to confirm this theory.

Why would cytokines cause sleep disturbances in patients? Natelson's research team hypothesizes that this is due to abnormalities in the pattern of sleep-disrupting and sleep-promoting cytokines in patients with objective measures of disturbed sleep. For example, cytokines that disrupt sleep include interleukin-4 and interleukin-10 (i.e., IL-4 and IL-10). Those that enhance sleep onset include interleukin-1beta and tumor necrosis factor-alpha (i.e., IL-1β and TNF-α). Natelson proposes to look at these cytokines periodically throughout the sleep/wake cycle to not only determine their level of production, but also their nocturnal rhythms. Then, he will try to correlate the cytokine levels with sleep study findings and symptoms.

Natelson suspects that cytokines are responsible for causing the sleep disorder in some CFS patients, and not the other way around.

How might cytokine production fit in with the symptoms of pain that most patients have? This is a complicated matter. TNF-α is a pro-inflammatory cytokine that produces pain, and IL-10 is supposed to block it (but if IL-10 levels are elevated, this could contribute to disturbed sleep). Ironically, the two cytokines that disrupt sleep were recently reported to be significantly low in the blood of patients with FMS (see box on next page for study details).

The AFSA-funded portion of this project is a tag-on to the NIH study and involves the assessment of two other important cytokines: interleukin-6 (IL-6) and interleukin-8 (IL-8). These two cytokines have been shown in more than one study to be elevated in patients with FMS.[1,2,3] Elevated IL-8 was found to correlate with pain intensity and duration of FMS symptoms. IL-8 is also believed to be an indicator of sympathetically-maintained pain (i.e., pain generated by a hyperactive sympathetic nervous system). IL-6 is thought to produce not only pain, but also fatigue and depressed mood. The table on page 6 provides a brief description of the role each cytokine plays in the body. In addition, a report that was just published on the low levels of IL-4 and IL-10 in people with pain (e.g., FMS) demonstrates the dual roles that some of these cytokines play in generating the symptoms of pain and fatigue. This could complicate the picture!

Functional brain imaging studies by Natelson and others also confirm that a dysfunction occurs in the central nervous system of both CFS and FMS patients, and this may likely be a result of abnormal cytokine production.[4] For example, brain blood flow evaluations in both FMS and CFS patients have shown a significant decrease in the brainstem area (which includes the pons) in both patient groups. In addition, a study by **Ali Gur, M.D.**, of Turkey, found that a greater drop in blood flow to the pons in people with FMS meant a higher level of

Cytokine Imbalance in FMS

Too many pain promoters & not enough pain relievers

Cytokines represent the link between the central nervous system and the immune system. When looking at their role in pain, these substances can generally be grouped into two main categories: (1) pro-inflammatory cytokines that produce pain (i.e., the bad guys) and (2) anti-inflammatory cytokines that reduce pain (i.e., the good guys). Previous studies in FMS have shown that an abundance of the "bad" cytokines exist in the blood, skin, and most likely, the central nervous system. This group of cytokines includes interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor alpha (TNF-α). The body also produces cytokines that counter the pain-producing effects of the "bad guys," such as interleukin-4 (IL-4) and interleukin-10 (IL-10), but a recent study by a German team shows that they are both low in people with FMS.[11]

Note that while IL-4 and IL-10 are considered the "good guys" when it comes to fighting pain, they are viewed as the "bad guys" when it comes to disturbing sleep. So, for conditions in which both pain and sleep disruption exist (i.e., most patients with FMS and CFS), clear-cut groupings of these substances into "good" or "bad" is not possible, at least not for IL-4 and IL-10.

The German study consisted of 40 patients with chronic widespread pain who did not respond to standard therapies (26 of whom had FMS) and 40 healthy controls. The amount of messenger RNA for IL-4 and IL-10 in the blood was substantially lower in the pain group than in the pain-free controls (but the blood levels of these cytokines were not directly measured). If this pattern of cytokine production can be duplicated, the authors believe that it will be useful for supporting the diagnosis of FMS and guiding the development of more effective therapies. (In recent years, commercially available kits for assaying cytokines have been developed, and their cost continues to drop, so they may soon be used for diagnostic purposes.)

This study's findings prompt an important question: What role do low IL-4 and IL-10 levels play in the development of FMS pain? Both IL-4 and IL-10 have been shown to greatly reduce pain in rats with injured nerves. In addition, IL-4 increases the number of opioid receptors on the nerves so that the body's natural opioids can lead to enhanced pain relief. If IL-4 is low, this could mean that fewer opioid receptors are present to "tame your pain." Prescription opioids may work well for some patients with FMS, while they may be inadequate for others. Fortunately, many therapies that target cytokine production are in the FDA-testing phase for the treatment of painful conditions. Yet, until the pharmaceutical industry is convinced that FMS pain is caused by a disruption of cytokines (due to the glial cells that produce them), these drugs will not be tested in FMS (for more details, see the discussion of Dr. Lorton's project on page 2).

interleukin-8 (IL-8) in the blood.[5] However, looking at the impact of depression, those patients without depressed mood exhibited even higher IL-8 levels than those who were depressed. Also, the presence of elevated IL-8 correlated with increased morning stiffness and sleep disturbance (based on questionnaires that asked about perceived sleep quality, rather than a sleep study).

After the second night in the sleep lab, the CFS patients in Natelson's study will be guided through an exercise test. The purpose of this test is to identify the effect that exercise has on nighttime sleep. In 2002, Natelson and coworkers published a report showing that exercise in CFS patients disrupts the body's normal 24-hour rhythm, which may help explain the common patient complaint that symptoms worsen following exertion.[6] The physiological reason for this phenomenon is not known, but evaluation of the patient's next night of sleep (the third night in the lab), including cytokine testing, may be key in understanding symptom flares.

Cytokines and Sleep

Studies in patients with obstructive sleep apnea syndrome or fatigued patients who complained of insomnia show substantial elevations in daytime secretions of TNF-α and IL-6, implying that a disruption of sleep causes a shift in cytokine production (less at bedtime and more during the day). With regards to IL-6, it is suspected to be associated with cognitive dysfunction, fatigue, feelings of exhaustion, and the symptom of pain. Thus, IL-6 may play a crucial role in generating the daytime symptoms of CFS, as well as those of FMS (one third of Natelson's subjects meet the criteria for FMS).

The above findings in people with sleep disorders, along with those in FMS that persistently show elevations in IL-8 (and oftentimes IL-6), are the main reasons for AFSA's tag-on study to Natelson's NIH project. In order to get a full picture of the cytokine mechanisms occurring in CFS patients, both IL-6 and IL-8 also needed to be assessed.

UARS will be Evaluated!

One of the greatest drawbacks of published studies involving sleep disorders is the common belief that apnea is a pulmonary-related sleep

disorder and all other sleeping difficulties (such as insomnia caused by upper airway resistance syndrome, UARS) are mental health problems. This dichotomous view is partly to blame for the lack of thorough sleep testing when apnea is not suspected (which is rarely entertained in young to middle-aged women who develop CFS or FMS). The result has produced a full body of medical literature that shows a disruption of cytokine production in patients with apnea, but none that pertains to people with UARS.[7]

Natelson's project is the first study funded by NIH to evaluate patients with subtle symptoms of sleep-related breathing to determine just how much of a problem they are in CFS. In other words, he will be evaluating the often overlooked condition of upper airway resistance syndrome (UARS). He is teaming up with pulmonary/sleep researcher **David Rapoport, M.D.**, at New York University, to determine if any of the sleep disruptions are occurring as a result of breathing impairments during the night, consistent with the diagnosis of UARS. A 2004 report by **Avram Gold, M.D.**, of Stony Brook University in New York reported that UARS may be the source of sleep disruption in almost all patients with FMS, many of whom also have CFS.[8] So, evaluating the breathing-related sleep disruptions in patients, as well as the changes in key cytokines, is an essential part of the project design.

Given that the majority of women attending a sleep clinic for evaluation of their insomnia complaints were found to have UARS in a previously published study, it is essential that this condition be assessed in order to fully understand the sleep disorder in CFS/FMS patients.[9] In addition, if UARS is found to be present in most of the CFS patients who have a sleep disorder, then future studies looking at the treatment of UARS and its impact on cytokines would be warranted.

Impact of Exercise

After the second night in the sleep lab, subjects will be put through an exercise test so that its effects on cytokines and the third night of sleep can be determined. The third night in the sleep lab will be the last night for the CFS patients. The healthy control subjects will also be tested, but their total sleep time will be restricted to the average time CFS patients spent in sleep during night two. This way, the cytokine productions for both the CFS patients and the healthy controls will be based on the same amount of sleep.

After the third night of sleep, the healthy controls will undergo the same exercise test that was administered to the CFS patients following the second night in the lab. Published research shows that sleep restriction in healthy subjects (two hours for one week) causes a disruption in cytokine production rhythm.[10] However, the added effects of exercise are not known, but its influence on sleep and cytokine production will be determined. **END**

Actions of Cytokines

Sleep Enhancers
- IL-1β
- TNF-α

When produced at night, they are helpful for sleep. If their production is shifted to the daytime, they can cause extreme fatigue.

Sleep Disruptors
- IL-4
- IL-10

If elevated, they may destroy sleep. Ironically, they have both been shown to be low in FMS patients.

Pain Promoters
- IL-1β
- TNF-α
- **IL-6***
- **IL-8***

***** These two cytokines are being measured as AFSA's tag-on project to provide a clear picture of what is happening. When IL-6 is secreted during the day, it causes extreme fatigue, depression and cognitive dysfunction.

Pain Relievers
- IL-4
- IL-10

The body increases their production to offset the pain-promoting cytokines. Of interest, a recent study indicated that the messenger RNA for these two cytokines was lower than normal in the blood of patients with FMS.

Summary: Note that the sleep-disrupting cytokines are also the pain-relievers. When sleep enhancers and pain-promoters are shifted to the daytime, many can produce severe fatigue. This is why Natelson is measuring all of the cytokines around-the-clock for a three-day/night period, along with looking at the influence of sleep quality and an exercise test on their production (both the quantity and time of day/night).

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A Special Message From the President

Your generous contributions have made it possible for many talented investigators to pursue FMS/CFS as their field of interest. Twelve years ago—before AFSA began funding projects—few universities had research programs devoted to the study of fibromyalgia. Now there are major centers focused on FMS research at universities around the world. While AFSA cannot take credit for all of the wonderful advances in the field, as a contributor and Member of AFSA, you should feel proud that you are making a difference! When I asked AFSA-funded investigators "What did the AFSA award mean to you?"—many said that it was an essential stepping stone to get them started on FMS research.

When AFSA began in 1994 as a small, all-volunteer organization whose only source of contributions were (and still are) from the FMS/CFS patient community, many had their doubts. Yet, you have been extraordinarily generous throughout the years. You have proven that the patient community *can* wield the power to direct research on your own condition! Now we are in the financial position to jump-start a research initiative on FMS sleep ... all due to the generosity of patients.

Every project described in this *Update* is expected to lead to important advances in our understanding of FMS/CFS, but the tissue donor bank represents an enormous step for rapidly expanding the science of this condition. Only two other medical conditions (Alzheimer's and Parkinson's disease) have such an elaborate tissue bank in place. It took a collaborative effort on the part of **Linda Watkins, Ph.D.**, **Dianne Lorton, Ph.D.**, and many of the scientists at **Sun Health Research Institute (SHRI)** to put this project together and to obtain major funding assistance from the National Institutes of Health (NIH). Although the NIH is expected to take on the brunt of funding for this project in the future, it never would have gotten off the ground had it not been for your donations.

As 2006 comes to a close, consider making a tax-deductible, year-end donation to AFSA. Don't worry about the slow mail service; checks dated for 2006 will be credited to that year. Please know that your contributions will be put to new and exciting research that will expedite finding the cause and, hopefully, the cure for fibromyalgia.

Wishing you happiness in the New Year,

Kristin Thorson

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Two Year Financial Recap

AFSA began raising money for research in March of 1994, and as of June 30, 2006, we have raised $1,746,456 and funded 30 projects on FMS/CFS. We continue to be an all-volunteer organization with no major overhead expenses (we receive all *in-kind* services **free** from **Fibromyalgia Network**). AFSA operates this way because we understand that you want *your* generous donations to go to research, not administrative expenses. Our financial summary for the past two years (July 1, 2004 to June 30, 2006) has been combined for ease of presentation and appears in the table below.

Over 90% went to our mission. AFSA has now funded 30 projects!

Ordinarily, AFSA strives to maintain a fund balance between $80,000 and $100,000—enough to ensure that any new and exciting proposal submitted to AFSA can be awarded. However, this year we have a larger-than-normal balance due to the enormous generosity of **Dyrna Hastings**, who put AFSA in her will. It is sad to lose a person with fibromyalgia, but her desire to see that more research is conducted on FMS has led to the development of our new sleep research initiative (as described on the front page of this *Update*). **END**

Financial Summary for July 1, 2004 to June 30, 2006

REVENUE		EXPENSES	
Contributions:	$ 444,453	Research Grants:	$ 97,528
Interest & Other:	$ 7,040	Educational:	$ 4,058
Note Cards:	$ 348	Operating Exp:	$ 10,491
Total Revenue:	**$ 451,851**	**Total Expenses:**	**$ 112,077**