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MISSION:

To encourage scientific research toward finding the cause of and cure for the 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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UPDATE

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Four Projects Funded in 2004!

During AFSA's eleventh year of operation, it awarded four research studies totaling **\$174,475**. The number of AFSA awards had reached a lull during the past two years, but in the beginning of 2004, we received four excellent proposals! **Roland Staud, M.D.**, has previously been funded by AFSA, but his new project represents an entirely different area of study. **Manuel Martinez-Lavin, M.D.**, is a published fibromyalgia syndrome (FMS) researcher in Mexico City who has never been funded by AFSA, but he presented a budget-conscious proposal to evaluate a genetic link to fibromyalgia pain that absolutely deserved to be funded. We also received a proposal by an investigator who is new to the field of FMS/CFS pain, **Linda Watkins, Ph.D.**, to study human cells in the central nervous system. This procedure has never been done before, although several animal models for painful conditions clearly implicate these cells in the development of chronic pain. Watkins is world-renowned for the fabulous advances she has made in the understanding of how the immune system communicates to the nervous system, so her interest in FMS/CFS pain should be viewed as a tremendous boost to this field of study. Finally, **John Stewart, Ph.D.**, who has been working on a project for AFSA to develop a new class of drugs, has been awarded a second grant to complete the final steps of his amazing work. The high diversity of projects funded by AFSA helps to ensure that every aspect of your condition is receiving the serious attention that it deserves.

As the National Institutes of Health (NIH) becomes more tight with its money (due to budgetary constraints under wartime conditions), more investigators are turning to AFSA for help with beefing up their applications to the NIH. Due to lack of funds, applications without preliminary data (i.e., those that have been seeded by AFSA) don't stand much of a chance at the NIH. There is a bright side to this picture: if AFSA continues to funnel money to researchers who are doing scientifically-based studies (instead of psychosocial projects), then AFSA will play a stronger role in the future direction of FMS/CFS research at the NIH level. In other words, the large-dollar NIH awards will more likely be given to the investigators previously funded by AFSA (because they will have high quality preliminary data to substantiate their theories), while the psycho-babblers will have a slim chance of getting the large awards from the NIH. Although the economy is tough on everyone, now is the time that patients have the greatest power to invoke influence over which FMS/CFS projects are eventually funded by the NIH.

It's been a long time since AFSA's last publication (the 60-page Special Edition), but AFSA is thankful for the people who continued to donate to our research-funding mission despite not being routinely prompted to do so. Although we try to keep costs down, this *Update* is long overdue! However, the description of the four projects awarded in 2004 is a strong affirmation to our continued perseverance to fund quality research for the benefit of patients worldwide.

END

The Role of Inflammation for Pain in Patients with Fibromyalgia Syndrome

Principal Investigator: *Roland Staud, M.D.*
University of Florida in Gainesville
Award Amount: \$75,000

If one could identify a chemical change in the blood of patients with fibromyalgia syndrome (FMS) during painful symptom flare-ups, it might serve as the basis for a disease severity marker and more effective therapies. This is the general premise of Staud's award, and it involves the tracking of cytokines, as well as other immunologically related substances. Elevated serum levels of specific cytokines were first identified by **Daniel Wallace, M.D.**, of UCLA, in a previous AFSA-funded project and similar findings have been found by other investigative teams.^{1,2,3} These studies involved measuring cytokine levels at a single point in time when patients were at rest and presumably not in a horrible flare-up (this is often referred to as the baseline value). In addition, Wallace found that the elevation of certain cytokines correlated with two factors: pain levels and duration of symptoms.

"One of the questions I am very interested in," says Staud, "is the cause for exacerbations or 'flares' of FMS pain. Much of this change is not easily detectable because of adaptive coping behaviors that most patients use." Staud comments that over time, these adaptations result in decreased function. The chemical processes that increase pain, and eventually lead to a loss of function, need to be identified and intercepted. Staud's project represents an essential step in identifying chemical changes that may be occurring in FMS patients. He will be analyzing the baseline levels of cytokines (and related substances) in patients and then follow them over time, particularly before, during and after painful

symptom flare-ups. In addition to analyzing over ten substances in the blood, Staud will be using objective pain measures, such as windup, to assess the pain levels and the degree to which a person's pain may be amplified by the central nervous system (CNS)—a process referred to as central sensitization.

"My main hypothesis," says Staud, "is that repetitive injury and/or inflammation is responsible for increasing the peripheral and central sensitization processes in FMS, and thus, the subsequent worsening of pain" (and other common symptoms). These injuries or inflammatory (as well as infectious) processes do not have to be dramatic to produce subtle "erosions" in the way the central and peripheral nervous systems operate. According to Staud, cytokines and related substances are used as a common chemical language for communication between the immune, brain and hormonal systems. He adds that if these cytokine chemicals are activated in FMS, it could influence the systems that regulate stress and make patients hypersensitive to stressful stimuli, such as infection and trauma.

Alterations in cytokines have the capacity to cause "downstream" changes in a person's pain sensitivity. The longitudinal study proposed by Staud will span two years, so the work on it will continue through to the end of this year. The goal of the project will be to determine if cytokines increase with symptom flares, and if so, which cytokine-related substances produce the most dramatic changes. Identifying which substances strongly correlate with symptom flares will provide valuable insight for the development of effective therapies and potentially produce markers for disease severity, which would be a tremendous asset for use in treatment trials. **END**

Translation from Animals to Humans: Are Chronic Pain States in Humans Associated with Glial Activation in Spinal Cord and/or Brain?

Principal Investigator: *Linda Watkins, Ph.D.*
University of Colorado in Boulder
with co-investigator: *Dianne Lorton, Ph.D.*
Sun Health Research Institute in Sun City, AZ
Award Amount: \$50,000

Fibromyalgia syndrome (FMS) is viewed as a form of pathological pain. Since sensory neurons relay pain to spinal cord neurons, which relay pain to the brain, past research has focused exclusively on neurons because the neurological system was blamed for the pro-

duction of pathological pain. Indeed, the neurons in the pain pathway are plastic; in other words, they are able to change the way they function. Over the years, a wide variety of such changes have been documented at various levels of the pain pathway, so it made sense for the drug development research to focus on correcting these plastic changes.

After a multitude of clinical drug trials, however, the sad conclusion is that drugs which target neurons do not control pathological pain, including FMS. How can this be? Watkins' extensive work in animals over the

past ten years points to a previously unrecognized player in chronic pain.^{4,5}

Just as a seething crowd incites boxers in the ring (getting them all worked up), brain and spinal cord cells called glia can incite neurons in the pain pathway. This drives the creation and maintenance of pathological pain. Unlike neurons, glia do not have axons projecting to distant sites, so they cannot operate like neurons to transmit signals to various regions of the body. Instead, when glia become activated, they operate by influencing the neurons in their neighborhood (i.e., nearby in the spinal cord and brain).

Not long ago, glia were ignored by pain researchers because they were not thought to influence neuronal function. This view is dramatically changing. New research implicates two types of glia in the creation and maintenance of pathological pain: microglia and astrocytes. This newly recognized role of activated glia, which function as powerful modulators of pain, has major implications for developing pain-controlling medications.

The problem is, activated glia have not been documented in humans with FMS. Although many studies have shown that cytokines are elevated in patients with FMS, and they are the primary substances produced by glia for communicating with neurons and other cells in the immune system, the glia have not been confirmed as the source of the cytokines. Definitive proof that activated glia are responsible for other pathological pain states (such as low back pain and various conditions involving nerve damage) is not yet available in humans, either. However, for every chronic pain condition that is easily studied in rats (i.e., a rat model exists), glial activation has been proven to play a key role in the production of the pain state. FMS does not have an animal model, so this correlation in rats cannot be demonstrated with the same degree of certainty that it can in low back pain and nerve damage.

The testing of new drugs begins in rat models and then progresses to the human clinical condition. The pharmaceutical industry has already begun to develop drugs that reduce glial activation (i.e., have a calming effect on these cells) and they are targeting conditions in which animal models exist. In this regard, FMS is at a distinct disadvantage because an animal model that represents the human condition has not yet been developed. The result is that the drug industry is not willing to take an expensive and potentially dangerous leap of faith with bypassing the animal testing phase and including people with FMS in their clinical trials.

With an animal model for FMS nowhere in sight, this study has many goals: (1) look for evidence of glial activation in the brain and spinal cord tissues of humans shortly after they have passed on, (2) compare the re-

sults found in deceased FMS patients with that of other donors with known chronic pain conditions in which an animal model has shown glial activation, and (3) also compare the results for all conditions to that of donor tissue of healthy, pain-free controls. If glial activation is found, it would provide a strong argument for testing drugs in FMS that target glial activation.

Due to the fact that human subjects have NEVER been assessed for glial activation (even in painful conditions where animal models involving glial activation are available), it is essential that other chronic pain states be used for comparison to build a bridge between animal models and their respective clinical conditions. How else can the results be interpreted—not just whether glial activation exists but also the degree to which it might exist? If Watkins' hypothesis is correct, then tissue from FMS patients will show activated glial cells, and in a roundabout way, it will aid with developing an FMS animal model. Of course, a successful outcome will also encourage the pharmaceutical companies to include FMS in their clinical trials ... even those that have or are just about to undergo human clinical testing. Shortly after AFSA awarded this grant, Watkins was successful in obtaining the supplemental funding from the NIH that is needed to thoroughly pursue all of the goals of this study.

As Watkins indicates, current medications that target neurons do not perform well for treating chronic pathological pain, such as that of FMS. "We believe that this failure is due to the fact that these drugs do not target glial function," states Watkins. AFSA is fortunate that Watkins has taken a strong interest in FMS so that this condition will not continue to be ignored by the vast majority in the pharmaceutical industry. **END**

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Association of Fibromyalgia with the Low Activity Catechol-O-Methyl-Transferase (COMT) Alleles

Principal Investigator: *Manuel Martinez-Lavin, M.D.*
National Institute of Cardiology in Mexico City
Award Amount: \$12,000

Prior research by Martinez-Lavin has demonstrated a prominent alteration in the autonomic nervous system (ANS) of patients with fibromyalgia syndrome (FMS). The ANS is the portion of the nervous system that regulates body temperature, blood pressure, heart rate, bowel and bladder function, and other vital processes. By working closely with the brain, the ANS helps regulate these functions that occur in the periphery (e.g., outside the central nervous system), and it also influences the production of a variety of hormones.

The ANS is divided into two branches: sympathetic and parasympathetic. These two branches have antagonistic (i.e., opposite) effects on most bodily functions. Sympathetic activity puts the whole body in a state of "high alert," whereas parasympathetic activity favors the promotion of sleep and digestive function. Using a technique called heart rate variability analysis,

Martinez-Lavin's group has demonstrated that people with FMS have a relentlessly hyperactive sympathetic nervous system.^{1,2} Based on his findings, Martinez-Lavin proposes that the key features of FMS (widespread pain and tender points) are largely produced by a physiological mechanism known as "sympathetically maintained pain."

The sympathetic nervous system communicates through the production of catecholamines, and these substances may be degraded by enzymes that have genetic anomalies that could potentially influence the entire ANS function. The three catecholamines used by the sympathetic branch are: dopamine, norepinephrine and epinephrine.

Catechol-O-methyl-transferase (COMT) is an enzyme that inactivates catecholamines. Martinez-Lavin proposes that a slight alteration in the genes that regulate the COMT enzyme could be the missing link to low pain thresholds in people with FMS. The idea for this AFSA-funded project stemmed partly from research

Continued on back cover ...

Your Dollars Go To Research

Our financial summary for the past fiscal year (July 1, 2003 to June 30, 2004) appears in the table below and as you can see, our mission is straightforward: we fund research. Less than 5% of your donations are used for continuing AFSA's operating costs because we are an all-volunteer organization and we have no overhead (we receive all *in-kind* services **free** from **Fibromyalgia Network**). A more detailed financial report will soon be posted on our Web site at www.afsafund.org. We are proud of our finances and will gladly send United States residents our IRS-990 report. All we ask is that you mail us a self-addressed, stamped envelope (9"x12" size) with \$3.85 postage so that we can keep expenses to a minimum.

AFSA is picky about the projects it funds. We don't fund behavioral studies or "do-it-yourself approaches" and all

**Over 95% went
to our mission.
AFSA has
now funded
27 projects!**

proposals must be budget-conscious. For unknown reasons, AFSA only received one application worthy of funding during the prior fiscal year (July 2002-June 2003). This created an increase in our fund balances, which were put to good use with the awarding of four exceptional grants during this fiscal year. As a result, our net fund balance dropped by \$65,833 to leave us with \$133,135 on

June 30, 2004. Your charitable contributions are definitely needed to help us continue with our research-funding mission!
END

Financial Summary for July 1, 2003 to June 30, 2004

REVENUE		EXPENSES	
Contributions:	\$125,137	Research Grants:	\$174,475
Interest & Other:	\$ 122	Educational:	\$ 8,165
Note Cards:	\$ 426	Operating Exp:	\$ 8,878
Total Revenue:	\$125,685	Total Expenses:	\$191,518

Started the year with a total fund balance of \$196,876 and ended it with \$133,135 to produce a deficit of \$65,833.

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Part 2: Cloning a Pain Neuropeptide Receptor

Principal Investigator: *John Stewart, Ph.D.*
University of Colorado in Denver
Award Amount: \$37,475

In 1998, AFSA initially funded Stewart with a small grant (\$24,560) to begin the process of cloning the receptor of the end fragment of substance P, referred to as SP(1-7) or simply SP-N. Details of the project and a 2003 progress report are on AFSA's Web site at: www.afsafund.org. SP-N is enzymatically cleaved off from substance P and has been shown to have pain-relieving properties. Coming up with medications that "act" like SP-N could generate a new class of effective pain-fighting drugs, particularly for combating the extremely high levels of SP that exist in the spinal fluid of people with FMS. Yet, in order for the drug industry to begin making "SP-N like" medications, the structure of the receptor at which it binds to for communication within the central nervous system must be known. Otherwise, it would be like trying to make a customized key for a lock without first knowing the type and structure of the lock.

Stewart has completed several major hurdles of this arduous task and this AFSA award represents the last

phase of the journey (Part 2). When AFSA initially funded the first part of this project, concerns were raised that it would take many years. Now that several years have passed, the end is sight! Stewart's tenacity, along with his experience as a biochemist with a keen understanding of FMS, has proven invaluable. **END**

CONTRIBUTE

Given that we have drained our excess funds, AFSA will need to restore its fund balances with new contributions to continue the flow of awarding quality research projects. Several patient-relevant proposals designed to advance the science of FMS/CFS are now under consideration. **People who have donated to AFSA recently will automatically be sent a copy of the next AFSA Update as a courtesy from AFSA.** Our intent will be to provide our donors with an update on the progress of recently funded projects as well as a description of new projects that we intend to award within the next three months. If you have not contributed to us lately, isn't it time that you did?

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published by **Jon-Kar Zubieta, M.D., Ph.D.**, of the University of Michigan. He showed that a single amino acid substitution in the structure of the COMT gene could alter pain processing and produce low pain thresholds in roughly 20% of the general population.³ This variant of the gene produces a “lazy” COMT enzyme that is unable to clear catecholamines properly. This in turn affects the functions in the ANS that are controlled by dopamine and norepinephrine, and also interferes with the body’s opioid-like analgesic substances.

In people with the normal or “effective” gene that codes for the COMT enzyme, their ANS works as it should and they have normal pain thresholds. Martinez-Lavin’s project will evaluate the gene that codes for the COMT enzyme to determine if the “lazy” variant is more prevalent in patients with FMS, compared to pain-free healthy controls.

At the October 2004 American College of Rheumatology (ACR) meeting, Martinez-Lavin provided preliminary data from this AFSA-funded study with roughly one fourth of his subjects evaluated. He found that FMS patients were more likely to have the gene that coded for the “lazy” COMT enzyme, while healthy controls tended to possess the version that coded for the “effective” COMT enzyme. Some overlap was present in the

data and clear-cut conclusions could not be drawn. However, three months after his ACR presentation, Martinez-Lavin suggested to AFSA that additional genetic testing be done because a January 2005 report by **Luda Diatchenko, Ph.D.**, of the University of North Carolina, indicated that other genetic variants coding for the COMT enzyme have been found.⁴ This latest study demonstrated that the susceptibility to pain in normal people was highly reliant upon the additional variations in the COMT gene. Does this mean that evaluation of the other genetic variants for the COMT enzyme could provide more conclusive data for FMS?

According to Matinez-Lavin, “A combination of variants give rise to a COMT enzyme that is even less effective in clearing catecholamines from the system and has a stronger association with pain perception.” Referring to the genetic structures detailed in Diatchenko’s report, he adds, “This model further advances our proposal of fibromyalgia as a sympathetically maintained pain syndrome.” Searching for the presence of the other genetic variants among the 40 FMS patients and 40 pain-free controls is the basis for the next grant that AFSA has awarded to Martinez-Lavin. **END**

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