The annual scientific session of the Myasthenia Gravis Foundation of America, Inc. (MGFA) was held on September 24, 2005 in San Diego, California at the Harbor Marriott Hotel. The session was organized by Dr. Gil Wolfe.

MGFA supports two types of research and educational grants. The Student Fellowship (formerly Henry R. Viets Fellowship) is targeted to healthcare professionals in training and provides monies to expose healthcare professionals to clinical or basic science research in myasthenia gravis (MG) via a short-term research project. The Post-Doctoral Fellowship (formerly Osserman/Sosin/McClure Fellowship) provides support for post-doctoral training in basic science or clinical research in MG. Both fellowships are designed to get promising healthcare professionals interested in MG so that these individuals will direct their future energies toward elucidating the cause, improving treatment and developing a cure for the disease. The meeting demonstrated the success of the fellowships. Several presentations were given by former Post-Doctoral fellows.

The meeting included discussion of two ongoing clinical trials on an MG-modifying agent and a discussion of the international clinical trial on thymectomy. There were thirteen presentations from around the world. Many of the presentations related to immunology, ocular MG or seronegative MG (clinical MG in individuals who do not have antibodies (Ab) against the acetylcholine receptor (AChR)). Brief reviews of the role of the immune system in MG, ocular MG and seronegative MG are provided to enhance understanding of the presentations.

The Role of the Immune System in Myasthenia Gravis

Myasthenia gravis is an auto-immune disease involving the site of communication between nerve and muscle, the neuromuscular junction. The lymphocyte class of immune cells are divided into two large groups: Thymus-derived lymphocytes (T-cells) and B-cell lymphocytes. T-cells are involved in cell-mediated immune responses in which cells attack immune targets. B-cells are responsible for producing antibodies that target specific parts of proteins called epitopes. Cells that process and present potential immune targets (also called antigens) to the immune system are called antigen presenting cells (APCs).

T-cells can modulate the activity of B-cells. MG is a T-cell dependent antibody mediated disease in which T-cells modulate the activity of B-cells that produce antibodies that are directed primarily against the AChR and secondarily against other sites (epitopes) at the neuromuscular junction. The antibodies binding to the AChR trigger a complement-mediated cellular immune attack against the neuromuscular junction. Complement is an immune-mediated chemical cascade that destroys proteins and injures or destroys cells.

Cytokines are proteins produced by the body that modulate the immune system. Interleukins (IL) are a class of cytokines that are secreted by lymphocytes. IL regulate the activities of different classes of immune system cells.
Interferons (IFN) are a different class of immune regulatory proteins. A recently recognized factor that can alter the immune response seen in different tissues is that cells have chemicals or factors bound to them that can alter the intensity of the immune response. A chemical called Daf is a local immune response modifying agent that is present on skeletal muscle cells. These cell-specific immune modifying agents may partially explain why some tissues, such as extraocular muscle, are preferentially involved in MG. Extraocular muscles (EOM) move the eyes and control the eyelids. When these muscles are not working in concert, a person can have double vision (diplopia) or drooping eyelids (ptosis).

Anti-C5 antibody treatment of passively-induced experimental myasthenia gravis
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The investigators examined whether they could decrease the intensity of MG in an experimental model of MG that is produced by injecting pathogenic anti-AChR antibodies into rodents (called passive transfer EAMG because the rodents were not proding antibodies; the antibodies were injected into them). They evaluated if blocking the complement cascade could reduce the intensity of the immune damage at the neuromuscular junction. They used antibodies directed at a key factor in the complement cascade (complement C5) activation in rodents with passive transfer EAMG. They chose to target C5 because it is involved in a late step of the complement cascade and the product of C5 activation enhances the inflammatory attack at the neuromuscular junction. Could interrupting C5 reduce disease? When given coincident with the pathogenic antibody McAb3, anti-C5 antibodies did prevent weakness. The investigators found less complement deposition and less NMJ structural changes in animals treated with anti-C5 antibodies. Even when anti-C5 antibody administration was delayed after starting McAb3 treatment, there was also a reduction in the severity of the disease. This work is interesting for several reasons. At the present time, there are no available anti-complement agents that can be used in people. A note of caution: the inflammatory attack at the neuromuscular junction is particularly prominent in this animal model of MG. It would be interesting to know if suppressing complement can suppress MG in other animal models of MG. The following study lends additional support to the importance of complement in MG. Perhaps this work and supportive work with other animal models of MG may encourage pharmaceutical companies to develop agents that inhibit complement activation.

The effect of Daf on T-cell activation and endplate destruction in experimental myasthenia gravis
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A large body of research on clinical MG and experimental MG (EAMG) has shown that the damage to the endplate is complement-mediated. Decay-accelerating factor (Daf) is produced by a diverse number of different types of cells, including skeletal muscle, and is present on the cell surface. Daf is an intrinsic complement-regulatory protein whose function is to limit local production of complement and activation of the complement cascade that leads to cell damage. In addition, Daf was recently found to modulate T-cell immunity by controlling T-cell interactions with the immune cells that present antigens to the T-cells (an early step in T-cell-mediated immune reactions). In this investigation, the authors compared the level of
complement activation, IgG deposition, and ultrastructural alterations at extraocular muscle and diaphragm neuromuscular junctions. Animals were assessed for acetylcholine receptor antibody production and T-cell activation. EAMG was induced by giving multiple administrations of purified Torpedo (an electric fish that was used to initially isolate AChR) AChR to 8-12 week old mice deficient in the gene that makes Daf (Daf1-/-) and also injecting AChR into littermates who had a normal Daf gene (Daf1+/+, these served as controls). Daf1-/- mice were weaker than the Daf1+/+ mice. All animals produced acetylcholine receptor antibody. All animals had C3 (an early component in the complement cascade) deposits at the endplate, whereas C9 (a later component of complement activation) deposition was more prominent on the endplates of the Daf1-/- animals. The neuromuscular junctions of EAMG Daf1-/- animals had more injury than the EAMG Daf1+/+ mice. T-cell activity was elevated in Daf1-/- mice. This study supports the role of complement activation in modulating the severity of EAMG. This study also demonstrated the novel interaction of Daf in T-cell activation. Therefore, complement inhibition may be an important target in the treatment of human MG.

The profiles of myositis autoantibodies present in the sera of myasthenia gravis patients in Taiwan
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This study was supported by the Chang Gung Memorial Hospital.

Although antibodies against the AChR (AChR autoantibodies) are responsible for the endplate damage seen in MG, some patients have antibodies against other parts of a muscle cell. The presence of antibodies directed against other elements of muscle may partly explain differences in disease severity among patients and also may explain why some patients suffer more extensive muscle degeneration. The authors studied patients from Taiwan who had MG to determine how often patients had the types of antibodies that are usually associated with diseases characterized by inflammatory breakdown of skeletal muscle. Inflammatory muscle disorders include muscle diseases called polymyositis and dermatomyositis. The authors studied a total of 32 patients with MG. All of the patients had antibodies against the AChR. They found that some patients (about one-third) also had antibodies directed against components of skeletal muscle that are usually associated with inflammatory muscle diseases. Other studies in the US and Europe have evaluated autoantibodies that targeted components of skeletal muscle other than the AChR, with the finding that many patients had anti-muscle antibodies (other than anti-AChR). However, the antibodies found in the other studies were usually not those associated with generalized inflammatory muscle diseases. It may be that Taiwanese patients have different antibody profiles and perhaps a slightly different disease. This study supports the notion that immune responses may be modified by ethnicity and perhaps by other factors so that MG may differ in some aspects for different groups of people in different areas.

Background for the Presentations about Ocular Myasthenia Gravis

Ocular MG refers to a variant of MG that involves only the muscles that control the eyelids and eye movements (extraocular muscles, EOM). Most patients with MG have involvement of extraocular muscles and about 20% of patients have ocular MG. A clinical challenge is to predict which patients who present with only extraocular muscle involvement will advance and have generalized MG and which patients will remain with ocular MG. A better understanding of why extraocular muscles are preferentially involved in MG would enhance our understanding of how this disease develops.
Genomic profile of muscle from passive EAMG rat
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The authors studied extraocular or eye muscles (EOM) and other skeletal muscles in rats with experimental autoimmune MG (EAMG) that was produced by injecting rats with antibodies directed against the AChR. They looked at how inducing MG changed the expression of genes in different muscle types. They studied EOM, diaphragm, and EDL (a specific extremity skeletal muscle). EOM had more genes with enhanced expression (unregulated) compared to EDL and diaphragm. The types of genes that were most prominently affected were those associated with modifying the local immune response to stimuli such as the antibodies directed against the AChR. Daf was one of the local immune modulating factors whose expression was altered in association with the induction of MG. EOM also showed a more prominent inflammatory response to the injected antibodies. It is not known whether the more intense immune response resulted from or was the cause of the enhanced expression of local immune modifying agents. Prior work from this laboratory had showed that altered levels of expression of chemicals that modify the intensity of the local immune response are correlated with how severely a type of muscle is impaired by MG. The local tissue chemicals that modify the local immune response may provide a new target for altering the course of MG.

Ocular myasthenia gravis in HLA transgenic mice immunized with acetylcholine receptor alpha subunit expressed in E.coli
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The authors produced MG in mice by injecting them with fragments of the AChR along with components of the bacteria E.coli. They found that the likelihood and intensity of MG in the mice depended upon several factors: 1) the surface markers present of the mice cells (dictated in part by the HLA characteristics of the mice), 2) the fragment of AChR used to induce MG and 3) the presence of bacterial proteins. The model developed in this study resembled clinical MG in that the mice had ptosis and impaired eye movements. The variable susceptibility of mice to develop EAMG based upon their HLA characteristics may explain why some patients are more prone to develop MG and why MG is more severe in some individuals. The MG model developed by this group may prove to be a good model system to study the effectiveness of potential MG treatments.

Background for Presentations on Seronegative Myasthenia Gravis

Antibodies are proteins produced by the immune system that bind to and target substances for destruction by the immune system. Antibodies are designed to target foreign substances such as bacteria. In patients with MG, antibody production is disturbed and antibodies are produced against self (i.e., antibodies target normal body proteins). The most common and the major pathogenic autoantibodies in MG are directed against the AChR on skeletal muscle.

Patients with antibodies against the AChR are considered to have seropositive MG. A fraction of patients with MG (about 20%) do not have anti-AChR antibodies. The MG in these patients is referred to as seronegative.
Many people with seronegative MG have autoantibodies against other components at the neuromuscular junction. The autoantibodies cause additional problems for patients with MG. Serum from patients with seronegative MG can be injected into animals and cause an MG-like condition. Immunoglobulins from seronegative patients bind to muscle cells, but not to AChR.

The most common target for antibodies in patients with seronegative MG appears to be a muscle protein called MuSK (muscle-specific receptor tyrosine kinase). MuSK is a muscle-specific protein that regulates how AChRs are incorporated into the neuromuscular junction. About 30-50% of seronegative MG patients are have antibodies directed against MuSK. The seronegative patients who have antibodies against MuSK are sometimes referred to in studies as MuSK+ or MuSK-MG. For comparison, patients with antibodies against the AChR are sometimes referred to as having AChR-MG.

MRI and clinical studies of facial and bulbar muscle involvement in myasthenia gravis and relation to steroid treatment
Authors: Vincent A, Farrugia M, Robson M, Newsom-Davis J, Anslow P, Matthews P, Hilton-Jones D
This study was supported by the Muscular Dystrophy Campaign of Great Britain.

Patients who have seronegative MG and who have antibodies against MuSK can be referred to as having MuSK-MG to distinguish them from patients who have anti-AChR antibodies (AChR-MG). MuSK-MG can be associated with severe bulbar and facial weakness and tongue atrophy. The authors studied 15 MuSK-MG patients and 15 AChR-MG patients selected to be similar in age, gender and clinical expression of disease. The authors used magnetic resonance imaging (MRI) to assess muscle wasting in facial and tongue muscles. They also evaluated the quality of the MRI signal associated with the tongue to evaluate for the presence of replacement of muscle cells by fat. MRI demonstrated thinning of the tongue and facial muscles as well as muscles involved with control of the eyelids in MuSK-MG patients and thinning of some facial muscles in some AChR-MG patients compared to healthy controls. The amount of the tongue that had altered signal suggesting fatty replacement was increased in both MuSK-MG and AChR-MG patients. The fraction of tongue with abnormal MRI signal correlated poorly with previous clinical scores (such as the QMG score and limb weakness assessed by manual muscle testing). For patients with MuSK-MG, the amount of abnormal MRI signal in the tongue correlated strongly with a new scoring tool that focused on eye, face and breathing muscle weakness. The amount of abnormal MRI signal in the tongue also correlated with the duration of treatment with prednisone at >40 mgs a day among the MuSK-MG patients. In summary, facial and eye muscle weakness, wasting and abnormal MRI signal was more commonly seen in patients with MuSK-MG compared to patients with AChR-MG. Some patients with AChR-MG had facial and tongue muscle weakness. The study found that facial weakness and wasting were associated with MuSK antibodies and, among AChR-MG patients, the duration of treatment with steroids (prednisone or cortisone-like drugs) at a dose of prednisone of >40 mgs a day. This study is important for several reasons. First, it increases the distinction between MuSK-MG and AChR-MG. Second, the amount of muscle wasting and degeneration correlated with the duration of high-dose steroid treatment.

Abnormalities on electrophysiological studies in MuSK-MG
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The authors studied patients with MuSK-MG and AChR-MG. People who had seronegative MG were diagnosed by the presence of electromyograph (EMG) findings that indicated MG. MuSK-MG patients had
more prominent facial involvement and often did not respond well to anti-ChE medications (anticholinesterase medications such as Mestinon). Patients with MuSK-MG were more likely to have abnormal facial muscle EMG signals. All groups of patients with MG (MuSK- and AChR-MG) were equally likely to have abnormalities in limb muscle EMG signals. Therefore, EMG studies of facial muscles appear to be useful for detecting MG in patients without anti-AChR antibodies.

Clinical Studies about Myasthenia Gravis

The effects of nutraceutical dietary intervention in myasthenia gravis
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The authors presented an unblinded, non-controlled study that purported to show benefit in 19 MG patients from treatment with different forms of micronutrients—sugars that are involved in glycosylating proteins.

Proteins are the structural building blocks of cells and also are the enzymes that are responsible for driving the chemical reactions that are needed for cells to function and survive. Proteins are composed of amino acids. After amino acids are linked together during a process referred to as translation (translating the genetic code contained in DNA into a sequence of amino acids) to make a protein, the protein undergoes several additional processes (called post-translational modification) that influence the structure and function of the protein. One of these processes is to attach specific sugars to the protein. The process of adding sugars is called glycosylation.

From the presentation, it was not possible to assure that all patients in the study actually had MG. Also, because both patients and the observer were unblinded, placebo effect could not be eliminated. For these reasons, it is not reasonable to use this study as an indication of the benefit of the glyconutritional agents studied. While glyconutritional therapy may be valuable, it requires careful study. Premature acceptance or adoption of this or any therapy based on small studies is a potential disservice to patients costing emotional disappointment and financial consequences. Nevertheless, positive results may warrant further testing using the approaches outlined by the FDA for establishment of drug safety and efficacy. The authors were urged to perform a controlled, properly blinded study before concluding that the studied agent was in fact beneficial in MG.

Bilevel positive airway pressure (BiPAP) ventilation in respiratory failure due to MG
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The authors presented their experience with using positive airway pressure (BiPaP) to improve breathing and to avoid artificial ventilation in patients with MG. There are several potential causes of respiratory failure. In patients with MG, weakness of the throat muscles that are needed to control the flow of air into the lungs can compromise breathing to the point that a person needs to have a breathing tube placed in the air pipe (trachea) and to be connected to a mechanical ventilator in order to breathe. In effect, the airway collapses, and placing the breathing tube into the airway compensates for the collapse of the airway. Another way of treating airway collapse is to provide continuous pressure to the airways to effectively “blow up” the airway to
keep it from collapsing. Positive airway pressure is achieved by the patient wearing a mask that blows out air to keep the airways open. One protocol for providing positive airway pressure is called Bilevel Positive Airway Pressure, or BiPAP.

The authors evaluated the effectiveness of BiPAP to reduce the need for intubation in MG patients with respiratory impairment. BiPAP was able to improve breathing sufficiently so that some patients did not need to be connected to a mechanical ventilator. BiPAP did not completely obviate the need for mechanical ventilation. Using BiPAP avoided intubation in 24/30 episodes of ventilatory failure in MG. This is important information because the appropriate use of BiPAP along with other techniques may improve the breathing care for people with MG.

Robotic-assisted thoracoscopic thymectomy for myasthenia gravis
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Thymectomy is the oldest surgical procedure used to treat MG. The thymus gland is located in the chest in front of the heart and is part of the immune system. The rationale behind thymectomy is that the thymus is involved in T-cell (thymus-derived lymphocytes) regulation, and T-cell regulation is disturbed in MG. By removing the thymus gland, it is hoped that an impetus for inappropriately activating T-cells will be removed. There are many different surgical techniques used for removing the thymus gland. Several surgical thymectomy techniques are minimally invasive, using endoscopic or robotic approaches. The advantages of minimally invasive techniques are that a person undergoes less injury (smaller surgical scars, less pain after surgery) and is likely to recover from the surgery faster. Disadvantages are that minimally invasive techniques may not completely remove all of the thymus gland. The equipment needed to perform the minimally invasive thymectomies and the training required to carry out this technique limit the number of sites where minimally invasive techniques are available.

The authors presented their experience using robotic technology to control surgical equipment that enters the chest through a few small holes in the chest wall. The robotic tools include devices for lighting the inside of the chest, cutting out tissue, and packing the tissue to be passed out of the chest through a small hole. The surgeon controls the robotic tools via computers and by wearing robotic gloves similar to those used to control some video games. The authors feel that they can achieve visualization (be able to see what they are doing) to an extent that is comparable to the visualization achieved with an open thymectomy, in which the sternum (breast bone) is cut in half and the rib cage spread apart to open the chest cavity. The authors have performed robotic thymectomies in about 60 patients. They felt that their results were comparable to those reported in studies using a traditional thymectomy, in which the sternum is cut in half. They reported remission rates approaching 40% at 18 months. At the present time, robotic thymectomy is not readily available in the US. It is worthwhile to follow this technology as it advances. Perhaps, in the future, robotic thymectomy will become the procedure of choice. Dr. Ruff’s opinion: at the present time, MG patients in the US who are considering thymectomy should probably place as their highest priority the track record of the surgeon performing the thymectomy, rather than searching out a person who does a specific technique.
Myasthenia gravis as a manifestation of the immune reconstitution inflammatory syndrome
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The authors described a case of MG that developed in a patient who was infected with HIV and who had AIDS. In general, MG is not part of the spectrum of AIDS. One might imagine that the immune suppression in AIDS would suppress the typical T-cell mediated immune response that causes MG. Perhaps that is why MG is rare in AIDS patients. In this case, the proposed mechanism was “immune reconstitution inflammatory syndrome” as a result of anti-retroviral therapy. In this syndrome, the immune system generates a vigorous attack that is usually directed against a target that would not normally be attacked. The syndrome may develop as a result of mutations in the immune surveillance apparatus. The immune surveillance apparatus is compromised by HIV attack of immune cells; consequently, patients who are infected with HIV are more likely to manifest this rare syndrome. When the immune system is compromised due to active AIDS, patients will not generate an immune reconstruction inflammatory syndrome. The syndrome is seen in people when AIDS has compromised immune surveillance and AIDS medications allow the immune system to manifest an inflammatory attack. Consequently, one way of treating the immune reconstruction inflammatory syndrome is to temporarily suspend AIDS medications (stop the anti-retroviral medications) until the immune reconstruction inflammatory syndrome has resolved. While this case describes a rare condition, it illustrates the importance of altered regulation of the immune system in the pathogenesis of MG.

Updates on Ongoing Clinical Trials of Mycophenolate Mofetil (CellCept®)
Presented by Dr. Donald Sanders, Duke University

Dr. Sanders described two mycophenolate (MMF) clinical trials in MG that evaluate the effectiveness of treatment and the side effect profile of the test drug. Mycophenolate is a drug that modifies the immune system. The goal of immune modulating treatment is to reduce the intensity of the immune response that is causing MG.

The first trial evaluates the utility of adding MMF to steroid treatment (with prednisone as the specific steroid agent). The aim is to evaluate the effectiveness of MMF as an agent that permits clinicians to treat MG with lower doses of glucocorticoid agents (drugs that act like cortisol and include prednisone and methylprednisolone; note that glucocorticoids are not the class of steroids that athletes are banned from using to enhance strength). The measures of effectiveness of treatment (outcome measures) are muscle strength, anti-AChR antibody levels and quality of life measures. This study has been going on for two years at 18 sites. The study duration for a patient is nine months. The study has now ended enrollment, and study results should be in by early spring 2006. The study was sponsored jointly by the FDA Orphan Products Development Program and the pharmaceutical company that produces CellCept®.

The second study is a randomized double-blind placebo-controlled study of MMF as a steroid-sparing agent. In this protocol, subjects are treated initially with prednisone until minimal manifestations are achieved, then MMF is added and the prednisone dose is tapered, as tolerated by the subjects. This study is still in the subject recruitment phase. No results are available as yet. This study is funded by the pharmaceutical company that produces CellCept®.
Thymectomy Trial Update
Presented by Dr. John Newsom-Davis, Oxford University, England

Thymectomy is the most commonly employed surgical treatment for MG. There has been an ongoing debate for many years about whether the procedure is effective in inducing remission of MG or reducing disease severity. The purpose of this international research program is to determine if the universally accepted and available surgical technique for thymectomy, trans-sternal resection, is more effective in treating MG than medical treatment alone.

The transternal surgical approach for thymectomy involves cutting through the breastbone to allow surgeons to have full direct visualization of the chest cavity to improve the likelihood that all thymus tissue will be removed. This project has been in development since 2000. Drs. Fred Jaretzki (current member of the MGFA Board of Directors and Medical Advisory Board), Henry Kaminski, Rick Barohn and Gil Wolfe (members of the MGFA Medical Advisory Board) were among the initial group of MG clinical researchers who initiated development of the thymectomy trial. They were joined by Dr. Gary Cutter from University of Alabama in Birmingham, who assisted with study design and who oversees the data collection and analysis. MGFA should take pride that this project has been approved for funding by the NIH.

MGFA provided early support to permit the investigators to get together to work out the initial version of the protocol. The protocol went through several revisions before the NIH was fully satisfied with its merits and procedures to provide funding. The thymectomy trial is designed to determine the efficacy of thymectomy in people with MG who do not have a thymoma. Note that people who have a thymoma need to have a thymectomy to remove the thymus tumor, which can compromise heart function and breathing. Therefore, people who have a thymoma should be considered for thymectomy independent of whether they have MG. To carry out the thymectomy trial, there are 70 potential centers: 33 in the US, 14 in the UK or Canada, and 23 around the world. These centers have all committed to participate and collect information in a uniform manner.

This is an important study that will evaluate the benefits and risks of thymectomy and help to determine when this surgery should and should not be done. The study should start in the next year. Progress reports of this extremely important clinical trial in MG treatment will likely be presented at the annual scientific session of MGFA, with more detailed updates at the MGFA international symposium to be held in Chicago in 2007.