brain
DECEMBER 2006 BRIEFINGS

RESEARCH DURING THE LAST 30 YEARS HAS PROVIDED SOME EFFECTIVE TREATMENTS FOR THE SYMPTOMS OF MYASTHENIA GRAVIS, WHICH CAN INCLUDE SEVERE MUSCLE FATIGUE. BUT THE TREATMENTS CAN HAVE SERIOUS SIDE EFFECTS, AND SCIENCE HAS YET TO UNCOVER THE ROOT CAUSES. HOWEVER, SCIENTISTS NOW ARE GAINING A MORE THOROUGH UNDERSTANDING OF MG THAT COULD HELP TREAT THIS DISORDER AND A SPECTRUM OF SIMILAR DISEASES THAT TURN THE BODY'S IMMUNE SYSTEM AGAINST SPECIFIC TISSUES.

MYASTHENIA GRAVIS

We all feel a little tired after exercise or a strenuous activity such as sweeping floors, dusting off coffee tables, or cleaning windows. But imagine if doing these chores made you so weak that you could barely move, see, or swallow.

About 100,000 people in the United States with the autoimmune disease myasthenia gravis (MG) face just such a risk each day. This disease, like other autoimmune diseases, turns the body's immune system on itself, causing it to attack certain tissues. MG mainly attacks voluntary muscles—those we can consciously control, such as when we walk, chew, smile, or look—and causes them to become weak and fatigued, possibly to the point of muscle failure. Although the severity of symptoms can vary, if left untreated, MG can lead to difficulty in swallowing, impaired speech, blurred vision, unstable gait, and, in some severe cases, respiratory failure.

Over 30 years ago, people with MG led very difficult lives, sometimes cut short from complications. Fortunately, research since then has yielded an enormous amount of information about the causes of MG and has provided some effective treatments.

Already research has led to:

- Advanced understanding of the communication process between nerves and muscle cells and how that process breaks down in MG.
- Information about how specific antibodies cause myasthenia gravis by interrupting the nerve-muscle communication.
- More treatment options, such as medications that counteract harmful antibodies or weaken the immune system just enough to keep MG symptoms at bay.

Researchers now know how the disease interrupts the action of the neurotransmitter acetylcholine (ACh), a chemical that relays the electrical signals from nerves to the muscle cells. MG causes the production of abnormal antibodies that damage or block many of the muscle receptors for ACh. This prevents ACh from binding to the muscle receptors and causing

▼ **MYASTHENIA GRAVIS OCCURS WHEN THE IMMUNE SYSTEM MAKES ANTIBODIES THAT DAMAGE OR BLOCK MANY OF THE MUSCLE'S ACETYLCHOLINE (ACH) RECEPTORS ON THE SURFACE OF MUSCLE CELLS. THIS PROHIBITS ACH FROM BINDING TO THE DAMAGED RECEPTORS AND ACTING ON THE MUSCLE, WHICH REDUCES MUSCLE CONTRACTIONS, LEADING TO WEAKNESS AND FATIGUE.**

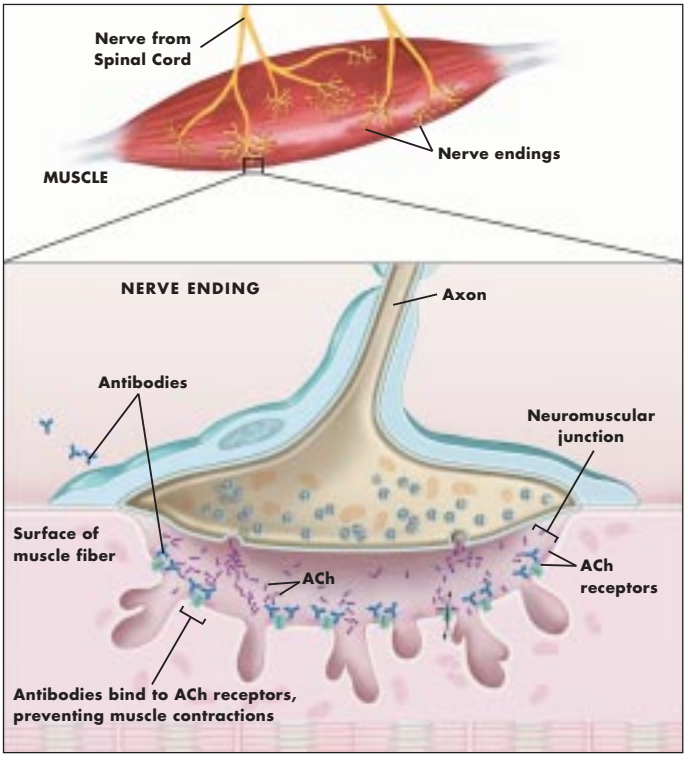

ILLUSTRATION BY LYDIA KIBIUK.

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the muscle to contract.

Scientists also have discovered that people with the disease have a reduced number of receptors on muscle cells for ACh. This impairs signaling between nerves and muscles, and causes muscles to easily and quickly weaken.

Knowing more about how the disease works has helped researchers develop effective treatments. Medications known as cholinesterase inhibitors block the action of an enzyme that breaks down ACh, thus increasing the amount of ACh that can act at the neuromuscular junction. Other drugs were developed to suppress the immune system and keep antibodies from attacking ACh or receptor proteins on the surface of the muscle cell.

Another therapy is to remove the thymus gland surgically. The thymus, which lies in the upper chest in front of the heart, plays an important role in the early development of our immune system, but it functions abnormally in adults with MG. Although scientists don't yet fully understand the role that the thymus plays in MG, they speculate that it may be responsible for causing immune cells to attack the body. Removing the thymus in people with MG has been shown to be beneficial in a large portion of patients.

Although current treatments can keep the symptoms in check, they may not help everyone. Even with treatment, people with MG face serious side effects, such as gastrointestinal problems and a higher risk of infection and bone weakening. More research is needed to improve our understanding of the disease processes in MG and to develop more targeted treatments.

While suppressing the entire immune system can reduce the symptoms of MG, it also can increase the likelihood of infection. New research is attempting a "guided missile" strategy to target only those immune cells that malfunction, rather than reducing the potency of the entire immune system. The strategy transfers genetic material into cells that stimulate a specific immune response from only those immune cells that are responsible for the disease in MG. These genetically modified cells then induce the faulty immune cells to die, sparing normal, healthy immune cells.

Other research efforts are seeking a deeper understanding—down to the molecular level—of how cells in the nervous system communicate and how this process goes awry. Answers to those questions could advance therapy not only for MG, but also for other autoimmune diseases, such as rheumatoid arthritis, thyroid disease, and diabetes. And make common chores much less of a health risk for the thousands of people with MG.

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