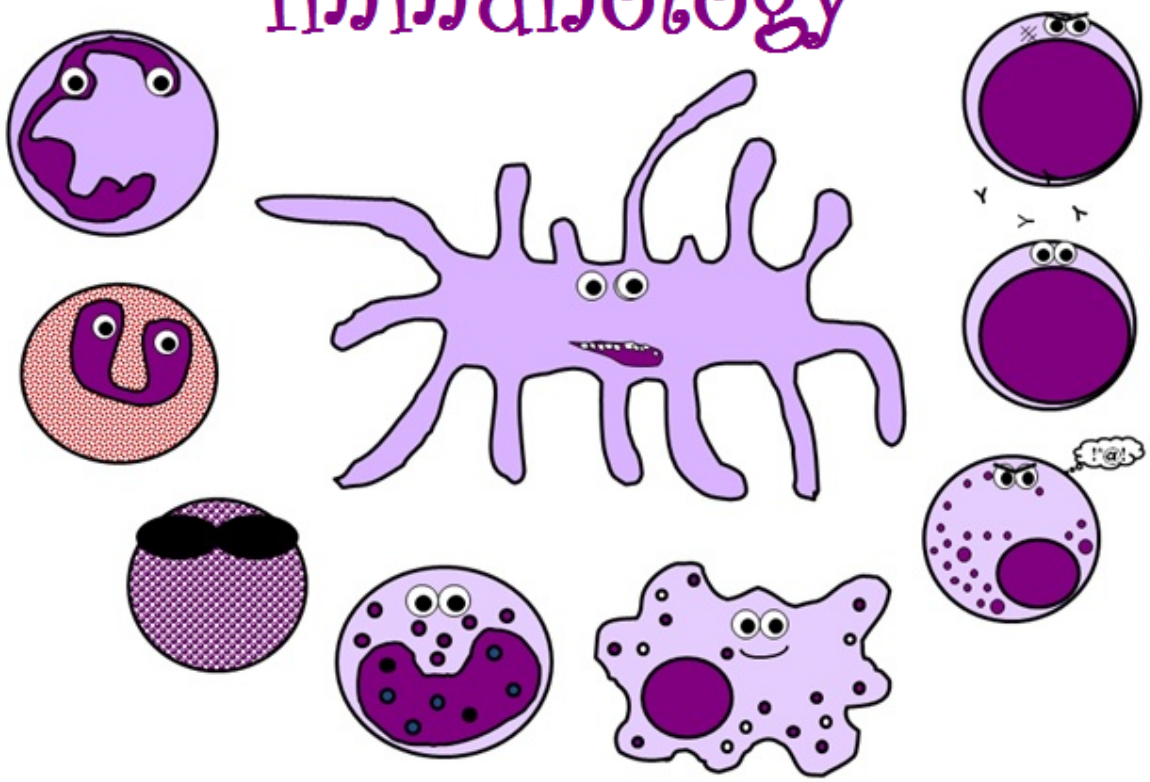
Immunology



◉Sheet ○Slides

Number: 19

Subject: Myasthenia Gravis

Done by: Hashim A. Mohammad

Corrected by:

Doctor: Issa Abu Dayya

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Before We Start:

- Everything in the book will be mentioned in the sheet, but for simplicity, we will focus on the essential-to-know information and put them in boxes on the right side of each paragraph. You still have to read the whole thing, but this is just to revise.
- This sheet is written based mainly on the book and to a lesser extent, the recording of section 2.

Myasthenia Gravis

In A Nutshell:

- Myasthenia gravis and Graves' disease are two main examples on autoimmune diseases caused by auto-antibodies directed at surface receptors.
- The main pathology in Myasthenia gravis is antibodies against acetylcholine receptors.

- The specific adaptive immune response can, in rare instances, be mounted **against self-antigens and cause autoimmune disease**.
- Injury to body tissues can result from antibodies directed against cell-surface or extracellular-matrix molecules, from antibodies bound to circulating molecules that deposit as immune complexes, or from clones of T cells that react with self-antigens.
- A special class of autoimmune disease is caused by autoantibodies against cell surface receptors. **Graves' disease and myasthenia gravis** are two well-studied examples.
- **Graves' disease is caused by autoantibodies against the receptor on thyroid cells for thyroid -stimulating hormone (TSH)**, secreted by the pituitary gland. In this disease, autoantibody binds to the TSH receptor; like TSH, it stimulates the thyroid gland to produce thyroid hormones.

- In **myasthenia gravis**, the opposite effect is observed: **antibodies against the acetylcholine receptor at the neuromuscular junction** impede the binding of acetylcholine and stimulate internalization of the receptor, thereby blocking the transmission of nerve impulses by acetylcholine. In addition, the presence of autoantibodies at the neuromuscular junction initiates complement-mediated lysis of the muscle end plate and damages the muscle membrane.

- **Myasthenia gravis means severe (gravis) muscle (my) weakness (asthenia).**

- How was this disease identified as an autoimmune disease?

  1- An immunologist immunized rabbits with purified acetylcholine receptors to obtain antibodies against this receptor. He noticed that the rabbits developed floppy ears, like the droopy eyelids (ptosis) that are the most characteristic symptom of myasthenia gravis in humans. Subsequently, patients with this disease were found to have antibodies against the acetycholine receptor.

  This proves that a disease similar to myasthenia gravis has developed in the rabbits that have acetylcholine receptor antibodies → Myasthenia gravis is caused by auto-antibodies against acetylcholine receptors.

  - This finding was a breakthrough in immunology in 1970s.
- Acetylcholine receptor was taken from the electrical eel (electrophorus electricus).

  2- In addition, pregnant women with myasthenia gravis transfer the disease to their newborn infants. As IgG is the only maternal serum protein that crosses the placenta from mother to fetus, neonatal myasthenia gravis is clear evidence that myasthenia gravis is caused by an anti-IgG antibody.

  Note: More recently, patients with myasthenia gravis have been identified who have autoantibodies against muscle-specific kinase (MUSK) rather than the acetylcholine receptor. MUSK is a tyrosine kinase receptor involved in clustering acetylcholine receptors; therefore, these autoantibodies also inhibit signaling through the neuromuscular junction.

  (This doesn't mean that the underlying pathology that we know is wrong. This just means that there's another mechanism of pathogenesis).

In A Nutshell:

- Rabbits with AChR-Abs develop something similar to MG.

Patients with MG have auto-Abs against the receptor.

→ MG is caused by auto-Abs against AChR.

- Mothers having MG pass it to the fetus, resulting in neonatal MG (this is temporary and lasts only for 2-3 weeks).
  - ➔ MG auto-antibodies are of the IgG type.

The Case of Mr. Weld

Mr Weld, a 71-year-old retired engineer, had been in good health and active all his life. **He developed double vision (diplopia)**. Initially, he did not want to seek medical attention because the double vision sometimes improved spontaneously. However, it gradually worsened over the course of 4 months and he finally scheduled an appointment with his physician. On examination, the doctor noticed that Mr Weld had **ptosis of both eyelids** so that they covered the upper third of the irises of his eyes. When the doctor asked Mr Weld to look to the right and then to the left, he noticed **limitations in the ocular movements of both eyes**, as shown in the figure.

The remainder of the neurological examination was normal. No other muscle weakness was found during the examination.

In A Nutshell:

Signs, symptoms and clinical findings:

- Diplopia
- Ptosis
- Limitations in ocular movements
- No enlargement of the thymus
- Elevated levels of AChR-Abs.
-

A radiological examination of the chest was performed, and it was normal. There **was no evidence in the radiograph of enlargement of the thymus gland**. A blood sample was taken from Mr Weld, and his serum was tested for antibodies against the acetylcholine receptor. **The serum contained 6.8 units of antibody against the acetylcholine receptor (normal less than 0.5 units).**

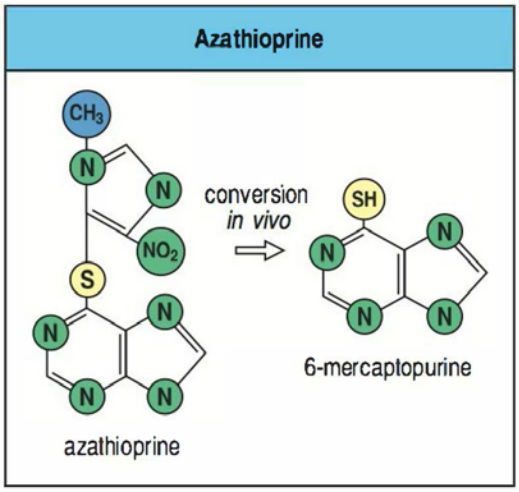
- Acetylcholine receptor levels are assessed by qualitative tests and quantitative test. Both has to be performed to confirm the diagnosis.

Mr Weld was told to take **pyridostigmine**, an inhibitor of cholinesterase. His double vision improved steadily but he developed diarrhea from the pyridostigmine, and this limited the amount he could take.

Three years later, Mr Weld **developed a severe respiratory infection**. Soon afterward, his ptosis became so severe that he had to lift his eyelids by taping them with adhesive tape. His diplopia recurred and his speech became indistinct. He developed difficulty in chewing and swallowing food. He could only tolerate a diet of soft food and it would take him several hours to finish a meal.

On examination the neurologist noted that Mr Weld now had **weakness of the facial muscles and the tongue, and the abnormality in ocular movements again became apparent.**
Remember: Getting a certain infection can be thought of as a trigger of auto-immunity.
His Treatment: Because of the diarrhea, Mr Weld was only able to tolerate one-quarter of the prescribed dose of pyridostigmine.

Note: Thymectomy in young adults with myasthenia gravis improves the status of the patient. But here he patient is 71-year-old, and his thymus is atrophied and replaced by adipose tissue, that's why thymectomy is not beneficial.



He also developed difficulty in breathing. His vital capacity (the amount of air he could exhale in one deep breath) was low, at 3.5 1iters. He was admitted to hospital and treated with **azathioprine**. Thereafter he showed steady improvement. His ptosis and diplopia improved remarkably and he was able to eat normally. His vital capacity returned to normal and was measured to be 5.1 liters.

- Myasthenia Gravis is a gradual process. The patient doesn't present with difficulty in swallowing in the early stages, but it mainly starts with muscle weakness that's worsened by activity.
- Being gradual encourages us as doctors to catch patients early and start treatment.
- This disease is type II hypersensitivity reaction (IgG-mediated).
- Type II hypersensitivity reactions are not only involved in myasthenia gravis but also in other autoimmune diseases, like immunohemolytic anemia, Goodpasture's Syndrome, and many others.

Some common type II autoimmune diseases caused by antibody against surface or matrix antigens		
Syndrome	**Autoantigen**	**Consequence**
Autoimmune hemolytic anemia (see Case 41)	Rh blood group antigens, I antigen	Destruction of red blood cells by complement and phagocytes, anemia
Autoimmune thrombocytopenic purpura	Platelet integrin GpIIb:IIIa	Abnormal bleeding
Goodpasture's syndrome	Noncollagenous domain of basement membrane collagen type IV	Glomerulonephritis Pulmonary hemorrhage
Pemphigus vulgaris (see Case 43)	Epidermal cadherin	Blistering of skin
Graves' disease	Thyroid-stimulating hormone receptor	Hyperthyroidism
Myasthenia gravis	Acetylcholine receptor	Progressive weakness
Insulin-resistant diabetes	Insulin receptor (antagonist)	Hyperglycemia, ketoacidosis
Hypoglycemia	Insulin receptor (agonist)	Hypoglycemia

- One of the most important side effects of cholinomimetics is diarrhea. That's why pyridostigmine caused diarrhea in the patient.

Questions:

1- How long do symptoms of MG last in infants?

1-2 weeks. Because the infant doesn't produce IgG antibodies, he/she just has antibodies from his/her mother. These IgG antibodies will last for several weeks, and then symptoms will end.

2- How does pyridostigmine work?
By inhibiting acetylcholine-esterase. This elevated the concentration of Ach in the synaptic clef, and it will be more likely for the endogenous Ach to bind to the receptor than the antibody.

3- Why is diarrhea a common side effect of pyridostigming?
Increased amounts of acetylcholine in intestines causes increased binding to muscarinic receptors in intestines, increasing intestinal motility.

4- How does Azathioprine work, any side effects?
It inhibits proliferation of B and T cells. Non-specific, makes patient more susceptible to infections. Long-term use is associated with lymphomas.

5- Why did severe relapse occur after infection?

Mechanism	Disruption of cell or tissue barrier	Infection of antigen-presenting cell	Binding of pathogen to self protein	Molecular mimicry	Superantigen
Effect	Release of sequestered self antigen; activation of nontolerized cells	Induction of co-stimulatory activity on antigen-presenting cells	Pathogen acts as carrier to allow anti-self response	Production of cross-reactive antibodies or T cells	Polyclonal activation of autoreactive T cells
Example	Sympathetic ophthalmia	Effect of adjuvants in induction of EAE	? Interstitial nephritis	Rheumatic fever ? Diabetes ? Multiple sclerosis	? Rheumatoid arthritis

- Immuno-privileged sites are the CNS and the eye.
- Read the mechanisms, effects and examples in the table.
- Super-antigens: antigens that can activated T-cells non-specifically without binding to the TCR. This results in polyclonal activation of T-cells.
  ex: Toxic Shock Syndrome. This is caused by S. aureus and it's common among women using tampons.

CASE 42 Myasthenia Gravis

The immune response turns against the host.

The specific adaptive immune response can, in rare instances, be mounted against self antigens and cause autoimmune disease. Injury to body tissues can result from antibodies directed against cell-surface or extracellular-matrix molecules, from antibodies bound to circulating molecules that deposit as immune complexes, or from clones of T cells that react with self antigens. A special class of autoimmune disease is caused by autoantibodies against cell-surface receptors (Fig. 42.1). Graves' disease and myasthenia gravis are two well-studied examples. Graves' disease is caused by autoantibodies against the receptor on thyroid cells for thyroid-stimulating hormone (TSH), secreted by the pituitary gland. In this disease, autoantibody binds to the TSH receptor; like TSH, it stimulates the thyroid gland to produce thyroid hormones. In myasthenia gravis, the opposite effect is observed: antibodies against the acetylcholine receptor at the neuromuscular junction impede the binding of acetylcholine and stimulate internalization of the receptor, thereby blocking the transmission of nerve impulses by acetylcholine (Fig. 42.2). In addition, the presence of autoantibodies at the neuromuscular junction initiates complement-mediated lysis of the muscle endplate and damages the muscle membrane.

Myasthenia gravis means severe (*gravis*) muscle (*my*) weakness (*asthenia*). This disease was first identified as an autoimmune disease when an immunologist immunized rabbits with purified acetylcholine receptors to obtain antibodies against this receptor. He noticed that the rabbits developed floppy ears, like the droopy eyelids (ptosis) that are the most characteristic symptom of myasthenia gravis in humans. Subsequently, patients with this disease were found to have antibodies against the acetycholine receptor. In addition, pregnant women with myasthenia gravis transfer the disease to their newborn infants. As IgG is the only maternal serum protein that crosses the placenta from mother to fetus, neonatal myasthenia gravis is clear evidence that myasthenia gravis is caused by an anti-IgG antibody. More recently, patients with myasthenia gravis have been identified who have autoantibodies against muscle-specific kinase (MUSK) rather than the acetylcholine receptor. MUSK is a tyrosine kinase receptor involved in clustering acetylcholine receptors; therefore, these autoantibodies also inhibit signaling through the neuromuscular junction.

This case was prepared by Raif Geha, MD, in collaboration with Janet Chou, MD.

Topics bearing on this case:
Humoral autoimmunity
Transfer of maternal antibodies
Mechanisms for breaking tolerance

Fig. 42.1 Autoimmune diseases caused by antibody against surface or matrix antigens. These are known as type II autoimmune diseases. Damage by IgE-mediated responses (type I) does not occur in autoimmune disease. In most type II diseases, autoantibodies bind to the cell surface or extracellular matrix and target them for destruction by phagocytes (often with the help of complement) and/or natural killer cells. A special class of autoimmune diseases is caused by autoantibodies that bind cellular receptors and either stimulate or block their normal function. Immune-complex disease (type III) is discussed in Case 37. T cell-mediated disease (type IV) is discussed in Cases 36, 40, and 53.

Some common type II autoimmune diseases caused by antibody against surface or matrix antigens

Syndrome	Autoantigen	Consequence
Autoimmune hemolytic anemia (see Case 41)	Rh blood group antigens, I antigen	Destruction of red blood cells by complement and phagocytes, anemia
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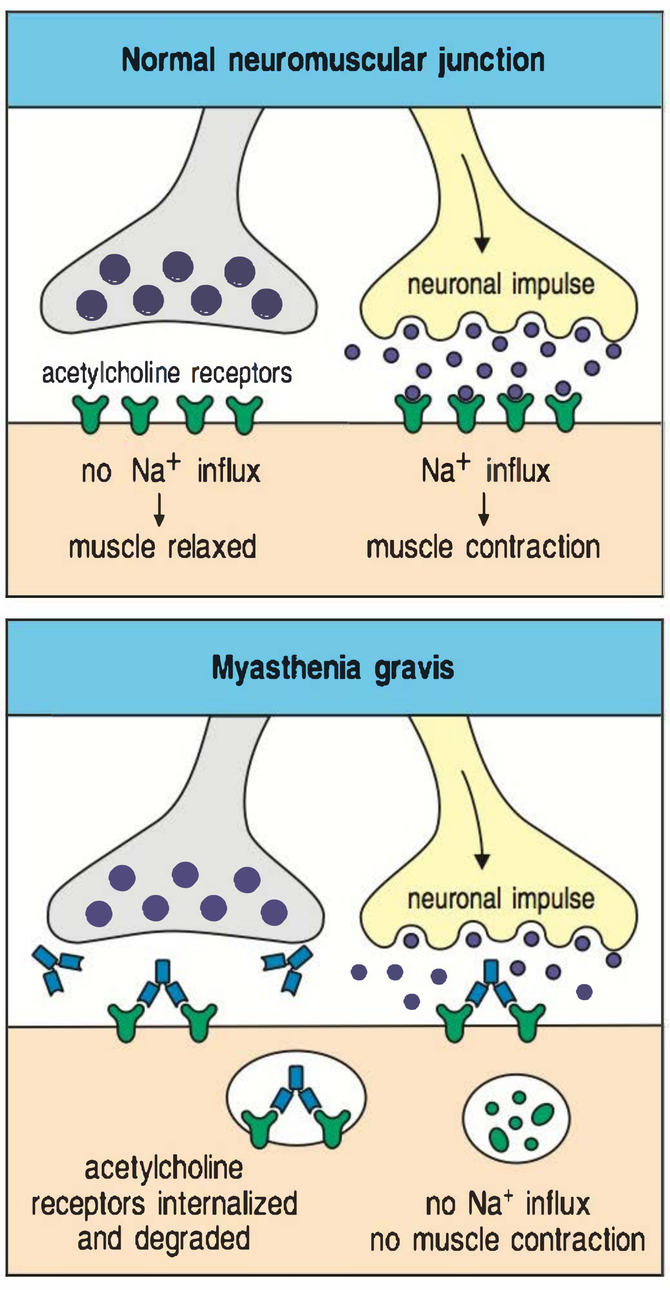


The case of Mr Weld: from floppy ears to droopy eyelids.

Mr Weld, a 71-year-old retired engineer, had been in good health and active all his life. He developed double vision (diplopia). Initially, he did not want to seek medical attention because the double vision sometimes improved spontaneously. However, it gradually worsened over the course of 4 months and he finally scheduled an appointment with his physician.

On examination, the doctor noticed that Mr Weld had ptosis of both eyelids so that they covered the upper third of the irises of his eyes. When the doctor asked Mr Weld to look to the right and then to the left, he noticed limitations in the ocular movements of both eyes, as shown in Fig. 42.3.

The remainder of the neurological examination was normal. No other muscle weakness was found during the examination.

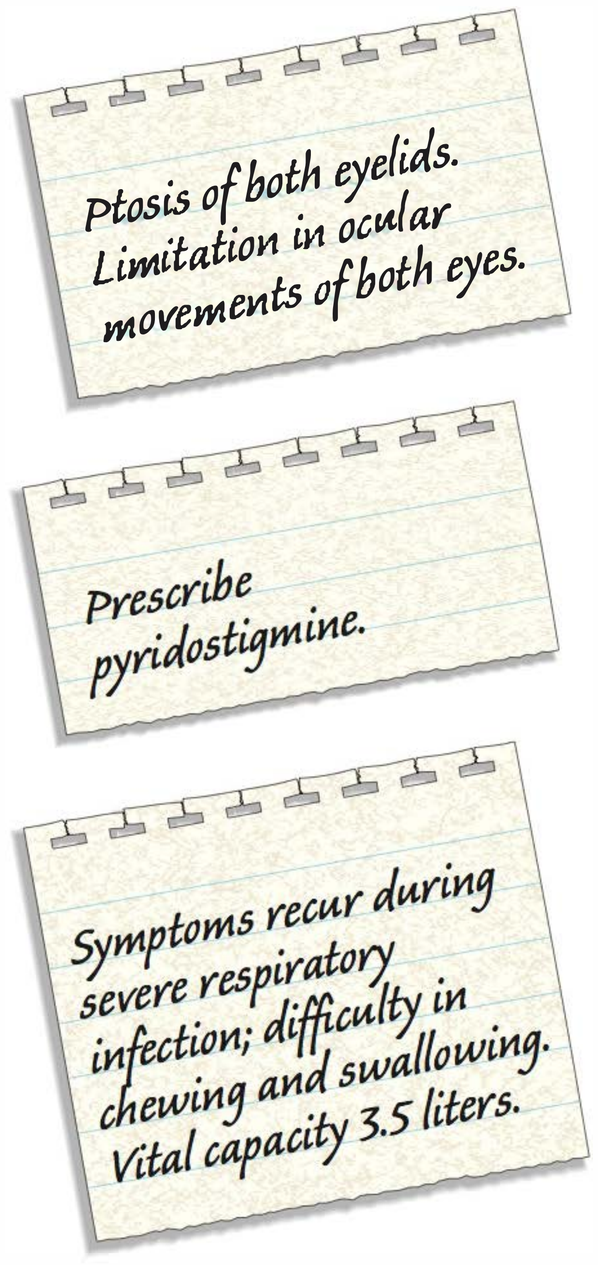
Fig. 42.2 Autoantibodies against the acetylcholine receptor weaken the reception of the signal from nerve ends that cause the muscle cell to contract. At the neuromuscular junction, acetylcholine is released from stimulated neurons and binds to acetylcholine receptors, triggering muscle contraction. The acetylcholine is destroyed rapidly by the enzyme acetylcholinesterase after release. In myasthenia gravis, autoantibodies against the acetylcholine receptor induce its endocytosis and degradation, and prevent muscles from responding to neuronal impulses.

A radiological examination of the chest was performed, and it was normal. There was no evidence in the radiograph of enlargement of the thymus gland. A blood sample was taken from Mr Weld, and his serum was tested for antibodies against the acetylcholine receptor. The serum contained 6.8 units of antibody against the acetylcholine receptor (normal less than 0.5 units). Mr Weld was told to take pyridostigmine, an inhibitor of cholinesterase. His double vision improved steadily but he developed diarrhea from the pyridostigmine, and this limited the amount he could take.

Three years later, Mr Weld developed a severe respiratory infection. Soon afterward, his ptosis became so severe that he had to lift his eyelids by taping them with adhesive tape. His diplopia recurred and his speech became indistinct. He developed difficulty in chewing and swallowing food. He could only tolerate a diet of soft food and it would take him several hours to finish a meal.

On examination the neurologist noted that Mr Weld now had weakness of the facial muscles and the tongue, and the abnormality in ocular movements again became apparent. Because of the diarrhea Mr Weld was only able to tolerate one-quarter of the prescribed dose of pyridostigmine. He also developed difficulty in breathing. His vital capacity (the amount of air he could exhale in one deep breath) was low, at 3.5 liters.

He was admitted to hospital and treated with azathioprine. Thereafter he showed steady improvement. His ptosis and diplopia improved remarkably and he was able to eat normally. His vital capacity returned to normal and was measured to be 5.1 liters.



Myasthenia gravis.

The defining characteristic of myasthenia gravis is a fluctuating weakness that worsens with activity and improves with rest. Normally, repetitive nerve stimulation during sustained physical activity results in the release of decreased amounts of acetylcholine with each successive stimulus; however, enough acetylcholine is released to achieve the desired muscle strength in healthy individuals. In contrast, patients with myasthenia gravis have fewer functional acetylcholine receptors as a result of the presence of anti-receptor autoantibodies. During repetitive nerve stimulation, the combination of fewer functional acetylcholine receptors with the physiologic decrease in neurotransmitter release results in muscular weakness.

Mr Weld experienced a common type of myasthenia gravis, called the oculobulbar form because it primarily affects the muscles of the eye. Older patients tend to have more generalized muscle weakness as well, and often have autoantibodies against muscle proteins in addition to anti-acetylcholine receptor antibodies. In very severe cases, difficulty in swallowing can cause the aspiration of food particles into the lung and impaired breathing, which may be fatal. Plasmapheresis (the filtration and removal of plasma from whole blood) can be used to remove the autoantibodies and treat a myasthenic crisis.

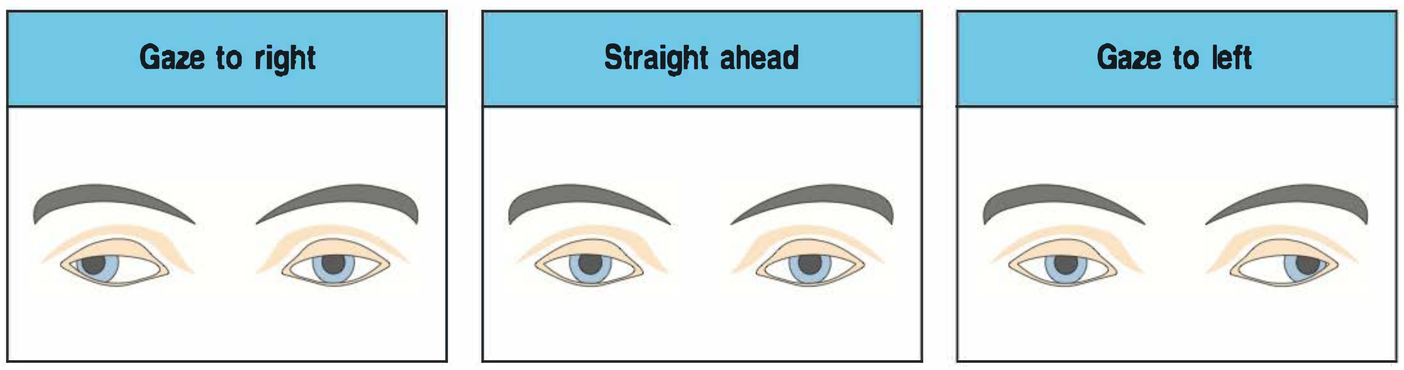


Fig. 42.3 Diagram of ocular movement limitation.

In younger people, the disease presents most often with weakness in the eye muscles. Chest radiographs of younger people with myasthenia gravis frequently reveal enlargement of the thymus gland; however, an association between myasthenia gravis and tumors of the thymus (thymomas) is more common in adults. Early removal of the thymus gland (thymectomy), particularly in those with thymomas, may lead to symptomatic improvement. Although the definitive mechanisms underlying the association between thymomas and myasthenia gravis are not yet identified, it has been hypothesized that neoplastic epithelial cells in the thymoma express selflike epitopes resembling proteins such as the acetylcholine receptor. In addition, thymomas have been found to have decreased expression of the autoimmune regulator gene (*AIRE*; see Case 17) and smaller numbers of regulatory T cells, indicating that an abnormal microenvironment within the thymomas results in impaired negative selection. However, as the occurrence of myasthenia gravis does not correlate with decreased expression of *AIRE* in the thymus, there are still unidentified factors that influence the development of myasthenia gravis in patients with thymomas.

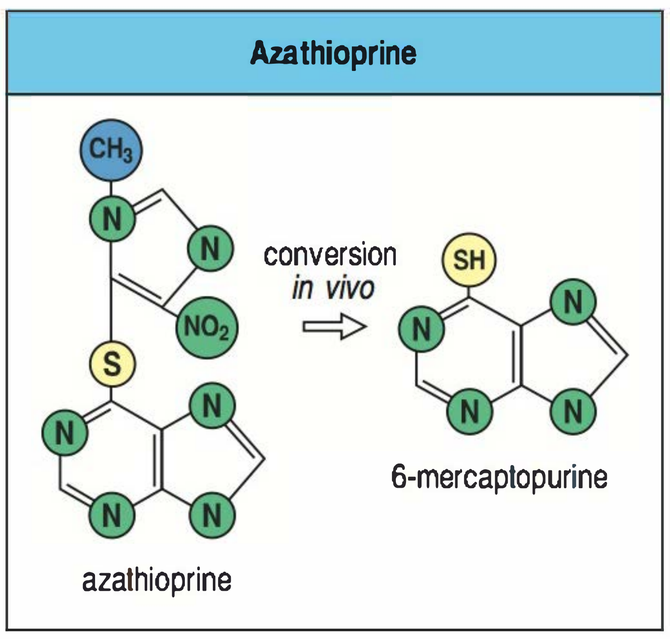


Fig. 42.4 The structure of azathioprine and its active product, mercaptopurine.

Questions.

1 *Newborn infants of mothers with myasthenia gravis exhibit symptoms of myasthenia gravis at birth. How long would the disease be likely to last in these infants?*

2 *Pyridostigmine is an ideal drug for the treatment of myasthenia gravis. It inhibits the enzyme cholinesterase, which normally cleaves and inactivates acetylcholine. In this way, pyridostigmine prolongs the biological half-life of acetylcholine. Unfortunately, it also causes diarrhea by increasing the amount of acetylcholine in the intestine. Acetylcholine binds to the muscarinic receptors in the intestine and increases intestinal motility. Because he could not tolerate full therapeutic doses of pyridostigmine and was getting worse, Mr Weld was given azathioprine (Fig. 42.4) and showed marked improvement. What did the azathioprine do? What would concern you about prolonged use of this drug?*

3 *Mr Weld had a severe relapse in his disease after a respiratory infection. Many autoimmune diseases seem to be triggered by infection, and relapses in autoimmune diseases frequently follow an infection. Can you explain how this might happen?*