chapter 16

First-Half Jameson

I had seen Dwight Jameson* several times on my television set before I saw him in my office for neurological consultation. He had not been particularly impressive in those few football games that I had half-watched. There was no question about his basic athletic skills. He was about an inch over six feet tall and weighed about one hundred ninety-five pounds. He combined strength and speed, and played free safety with a degree of abandon that had won him some consideration as an All-American pick while in college. But his professional career had never been peppered with such success. During his rookie year he had played on special teams, coming into the games for kick-offs, kickoff returns, and the like. He made the starting defensive lineup in his second year. By the time he arrived in my office, his fifth season had drawn to a close and it appeared that his career was also just about over. He had been back on the special teams for the last half of the season.

The one time I had watched him play that fall, his demotion seemed justified. Not in my mind; I do not pretend to be a judge of professional football talent. That had been the judgment of those ex-players who announced the games and then talked on about the plays and the players between plays, between halves, after the games, ad infinitum, ad nauseam.

*This is not his real name; that is protected by patient-physician confidentiality.

It seems that Dwight Jameson had acquired a bad reputation. He was not a dirty player who tried to hurt key members of the opposing team. This all transpired well over a decade ago when such "punishment" was still considered good form, a part of the macho image of professional football and its practitioners. His reputation was for not making the "big play," especially late in the game. To be more precise, he had developed a talent for letting the big play, invariably a long pass for the winning touchdown, go over his head and into the hands of the opposing team. A few such plays resulting in fourth-quarter losses created his reputation and eventually reduced him to the rank of special team player.

One of the announcers remarked facetiously that Jameson was halfway to being an all-pro.

"Which half?" the straight man of the announcing tandem asked.

"The first half," the ex-linebacker quipped. He then went on to explain that Jameson always looked great in the first half, when the game was not yet on the line. It was toward the end of the game that he fell apart. Good old First-Half Jameson, half of an all-pro. Had he played for a more prominent team his nickname might have rivaled that of Wrong Way Corrigan, the pilot who supposedly took off in New York heading for California and landed instead on the other side of the Atlantic.

The implication was clear. Jameson was not man enough to do what he had to do when the chips were down. In college, he'd had a different nickname; he'd been called Sleepy Jameson. I assumed that had reflected a habit of sleeping through classes.

After the game I gave the comment no further thought. Jameson was little more to me than a bit player in a game I half-slept through on a dreary Sunday afternoon, killing time in between watching the Chicago Bears and having dinner. The kind of day when it was too cold or too wet to hit a bucket of golf balls.

Then Dwight walked into my office. He had been referred to me by his cousin, who had been a resident in internal medicine at our hospital seven or eight years previously and had spent a

couple of months learning some neurology with me. The cousin knew enough about medicine and neurology to suspect that something was wrong with Dwight, but couldn't put his finger on it precisely, so referred Dwight to me. It was late in December and his team had lost too many games in the fourth quarter to be in the play-offs.

I did not recognize him. I don't think I would have if he had walked in wearing shoulder pads and a football helmet. I also did not recognize his name when I saw it on his chart and introduced myself to him. Such is fame. As it was, his name did not click in until he told me what he did for a living. He was a safety in the National Football League, he told me.

Dwight Jameson, I thought to myself. Not exactly a household name. He wasn't a free safety anymore. He played only on special teams, but he still thought of himself as a safety and I wasn't one to contradict him. Then the significance of his nickname, First-Half, hit me. And so did the diagnosis. Or at least a possible diagnosis, a disease to be considered, to be eliminated. A prominent part of his differential diagnosis. That disease was myasthenia gravis.

Put simply, myasthenia gravis means grave weakness of the muscles. It is not exactly a diagnosis that conjures up images of happy endings. For the first decade or so of my professional life, happy endings for my patients with myasthenia gravis had been few and far between. Many of those patients had fared quite poorly. Their prognosis had been truly grave and their management had been a nightmare both for them and me. As I recall, I had even taught Dwight's cousin my aphorism on myasthenia, an aphorism designed to help my beleaguered residents learning how to take care of these patients: whenever there is a crisis in a patient who has myasthenia gravis, no matter what you decide to do, the chances are greater than fifty-fifty that the patient will get worse. No matter what you do, the odds are against you. That is the nature of the disease.

In my residency, I had been taught another rule. If there is a neurologist you really dislike, refer all your myasthenic patients to him. Let him make all of those bad decisions.

Myasthenia gravis is a disease of the neuromuscular junction. The neuromuscular junction is the crossroads at which the motor nerve innervates the muscle. This junction is also known as the motor end plate and is a highly specialized structure that is surprisingly constant in both structure and function throughout most of the animal kingdom. The motor end plate evolved as a good way to convey orders from the nervous system to the effector organ, the muscles. It developed long ago and has undergone only minor evolutionary changes in the last several hundred million years. The neuromuscular junction should be seen as a very old structure carrying out a very old set of functions. This junction relays messages from one cell to another, one of the key problems to be solved by complex, multicellular organisms. In a way it is very much a modified synapse. The synapse is the specialized structure by which neurons communicate with each other. In a motor end plate a motor neuron communicates with a muscle cell. The neuronal structure makes up the presynaptic portion, which is separated from the muscular part, the postsynaptic receptor membrane, by a space. This space is called the synaptic cleft.

The job of a motor nerve is to convey messages from the central nervous system to the muscles. The message travels as an electrical impulse down the axon of the nerve leading from the cell body to the nerve terminal. Once the terminal is reached, the cleft between nerve and muscle must be crossed. This is not breached by electricity but by a specific chemical agent, acetylcholine, which is released by the nerve ending. This chemical neurotransmitter then crosses the synaptic cleft and interacts with the postsynaptic receptors generating another electrical impulse or action potential, and initiating that series of chemical reactions that produce contraction of the muscle. This is what happens in humans, what happens in eels, and what happens in all the species between the two. It is a solution to the problem of delivering the right message to the right place at the right time. It was such a good solution that no better one has yet to evolve despite millions of year of descent along a variety of separate lines.

Why all this complicated electrochemical stuff? Wouldn't simple electrical transmission be easier? Perhaps, but chemical transmission has its advantages. With it, messages can only cross the synapse in one direction, from the presynaptic nerve terminal that releases the chemical to the postsynaptic receptor that binds with it. There is no back talk. Besides, chemical transmission came first. Cell membranes of primitive organisms without specialized nerve cells or muscle cells respond to chemicals and have developed specific structures designed to respond to specific chemicals.

Two variations on this primitive sequence have evolved and continue to function in all complex animals, including humans. One is the endocrine system; the other is the nervous system. The entire endocrine system is based on chemical transmission of messages. Hormones are released and travel throughout the entire body, and are only taken up and act on those cells that have specialized membrane receptors for that hormone. Specificity of the message depends on two factors: the chemical structure of the messenger and the pattern of cells with receptors that respond to that message. The pituitary gland releases a specific polypeptide to increase production of steroids by the adrenal glands. That polypeptide goes everywhere in the body. Most cells are oblivious to it and their membranes have no receptors for it. Not so the adrenal gland; here the polypeptide is taken up and does its job. That is the essence of the endocrine system at work. In asking the question of which came first, the nerve or the receptor, the answer is the receptor and the chemical.

In the endocrine system, the message carrier is called a hormone; in the nervous system, a neurotransmitter. In the latter system, the transmitter is not set loose upon the entire body to find the right receptor; it is delivered to the correct place by the correct nerve. That allows every nerve to use the same transmitter for only one muscle cell to receive each specific message. The neuromuscular junction is one of the oldest of these delivery systems. The same neurotransmitter chemical, acetylcholine, carries out that same function in every human muscle, and in every muscle throughout most of the animal kingdom.

Once acetylcholine has hit the postsynaptic receptor and triggered the ensuing process in the muscle, it has to get out of the receptor. It is the initial interaction between acetylcholine and its receptor that initiates the process of muscle contraction. Remaining there initiates nothing more. In fact, it prevents new interactions and as a result causes weakness and paralysis. This is how the poison curare works. It enters the bloodstream, like a hormone, is distributed to the body's neuromuscular junctions, and once there binds to the postsynaptic receptor—and stays there. Acetylcholine can no longer get in. That means no new interaction, no initiation of muscle contractions. The result is paralysis leading to respiratory failure and death. All from a little chemical that slips into the acetylcholine receptor and won't get out. Curare's uniformly deadly effects demonstrate the unity of this system throughout the animal kingdom and also point out the most vulnerable part of the entire system.

Once the process is triggered, the acetylcholine is released from the receptor. This allows the next molecule to enter the receptor so that the muscle can be stimulated to contract again. That process is where many natural poisons work. Evolution got started devising these poisons long, long ago, and the acetylcholine receptor has been the target for many of them. Many snake poisons, such as bungaro toxin, the toxin of the deadly bungarus snake, function in the same fashion and are just as deadly. This knowledge is not new. Claude Bernard, the greatest of all experimental neurophysiologists, studied curare in the 1850s and localized its site of action to the neuromuscular junction.

Life then depends on the next molecule of acetylcholine being able to get into that receptor. The previous molecule has to go. And go it does. Acetylcholine is destroyed by an enzyme called acetylcholine esterase. This enzyme cleaves acetylcholine into two small molecules and reopens the receptor. The neuromuscular junction is back in business again. It is ready for the next jolt of acetylcholine.

The acetylcholine that acts on the motor end plate seems to carry out two separate functions. This process has been discussed

already in this book in relation to two other diseases: the poliomyelitis of Wilma Rudolph (Chapter 11) and Lou Gehrig's motor neuron disease (Chapter 15). Acetylcholine both initiates contraction of the muscle and performs a trophic, or growth-stimulating, function that keeps the muscle alive and well. Wilma Rudolph wore braces because polio had injured some of her motor neurons so severely that they lost their trophic capabilities and the muscles of her leg became wasted. As a result, her leg was crooked for years until recovery occurred and the muscles were stimulated to grow back. Lou Gehrig's nerves died off, one nerve cell at a time, day after day after day, and his muscles became weaker and weaker. Deprived of all trophic input, they also became more and more shrunken, in a disease that became graver than grave.

Myasthenia is far different in other ways, however, from either polio or amyotrophic lateral sclerosis, or any other disease for that matter. It does not begin by causing permanent weakness that progresses. It may not ever progress in the usual sense. It fluctuates. The symptoms come and go. Sometimes they are there. Sometimes they aren't. Sometimes the acetylcholine can get its message through. Sometimes it just can't. The major factor in this intermittent function is often the influence of exercise, or muscular activity. The more a muscle is exercised, the more likely it is to become weak—conditioning in reverse.

The patient feels fine in the morning. He is strong. There is no evidence of any weakness. He looks, feels, and acts as if he is normal. And he is. All of his muscles are reacting quite normally to the messages being relayed to them. He goes to work. He feels fine. He works a couple of hours. He is still okay; but then the system begins to fail. Not everywhere at once. It is not a matter of generalized weakness either slowly or suddenly appearing. It is usually just one or two muscles that become weak. Often it is the eyes that go first. One eyelid begins to droop. Sometimes even both do. In neurological circles this drooping is called ptosis. Ptosis is caused by weakness of the muscle that elevates the upper eyelid. This is one of the few muscles that is at work almost one hundred percent of the time

during the waking day. Ptosis on one side can make the patient look as if he has something wrong with one eye. The drooping of both eyelids, of course, can give the patient a sleepy appearance.

Bingo times two! I may be slow on the uptake sometimes, but this I recalled. Dwight had had another nickname, "Sleepy," and it hadn't come from sleeping in class.

Ptosis merely resembles sleepiness because of the patient's inability to keep his eyes open. It is not normal sleepiness. The patient is not tired; his eyelids are weak. There is a big difference. The weakness does not end there. The muscles that control eye movements and keep the two eyes looking at the same place at the same time are also working constantly. If their balance becomes upset, the two eyes no longer track identically. The entire visual-motor system is designed to get the same image to the same place at the same time so the brain can see one image. If the messages from the two eyes do not get to the same visual cells at the same time what is delivered is no longer interpreted as a single image but as two images. Two images means that there are two objects out there. Every line on a printed page becomes two. That long pass heading for the end zone becomes two footballs arcing down the field. Double vision, also known as diplopia.

I asked Dwight Jameson why he had so much trouble in those fourth quarters.

"You sure don't beat around the bush," he replied.

I persisted.

"I see too many footballs," he finally admitted.

"How many is too many?" I asked.

"Two," he said softly.

"That's one too many," I agreed.

Dwight saw two footballs late in the game when he and his body were becoming fatigued.

But only on long passes," he insisted. That was not much of a consolation to his coaches or teammates or the fans. Getting beat on long passes was precisely what was not supposed to happen to a free safety. No long bombs. It was also precisely the result myasthenia would produce. Tracking a fast-moving object

requires precise, continuous firing of the muscles that move the eyes. Continuous acetylcholine receptor interactions in rapid succession. Any failure at all would mean diplopia. Two footballs. Six points for the other side.

Back to special teams.

I looked at Dwight's face, at his eyes. He looked normal. They looked normal. There was no ptosis. Both eyes were in perfect alignment. I instructed him to follow the tip of my pen and then moved my pen back and forth. His eyes followed it perfectly. Minute after minute.

"After a game," I inquired, already anticipating the answer, "do your eyelids droop?"

He looked at me curiously. Maybe I wasn't such a fan. "That's why I was called Sleepy, because I look sleepy after a game. I'm no more sleepy than anyone else, I just look more tired. My eyes droop."

"And the next day your eyes look fine."

"They look fine by the time I have dinner and relax for a while. I don't even have to go to sleep. I just close my eyes for a few minutes."

Weakness and recovery. The hallmark of myasthenia gravis.

"Have you always been called Sleepy?" I asked. Was this a lifelong condition or something new?

He said the drooping had begun in college, during his senior year.

"Onset during his senior year in college," I wrote in his chart.

Intermittent weakness, weakness followed by recovery, is the key characteristic of myasthenia gravis. Recovery occurs when the muscle relaxes, when fast rates of firing are no longer required. Sleepy Jameson clearly had a history of weakness brought on by exercise and relieved by rest.

Myasthenia, of course, is not a new disease. Its peculiar intermittency has allowed modern physicians to diagnose it in retrospect in the writings of physicians from previous eras. The first description is usually credited to the English physician and anatomist Thomas Willis, who also described the circle of blood vessels at the base of the human brain that now carries his name,

the circle of Willis. He called the disorder *paralysia spuria non habitualis*, paralysis that was spurious and not fixed or habitual. His description, written in 1683, includes the following details: "The patients are able at their first rising in the morning to walk, move their arms, or to lift up a weight with strength but before noon . . . they are scarce able to move hand or foot. . . . I have now a prudent and honest woman in cure, who for many years has been obnoxious to this kind of bastard palsy, not only in the limbs, but likewise in the tongue. This person for some time speaks freely and readily enough, but after long hasty or laborious speaking, presently she becomes as mute as a fish, and cannot bring forth a word, and does not recover the use of her voice till after an hour or two. . . ." Shades of Dwight Jameson.

There is another case of some historical interest that comes down to us from the nonmedical literature, and the subject has become known as the first American with myasthenia. This patient was a Native American chief named Opechankanough. When he was over seventy, he became incapacitated by severe weakness and had to be carried about on a litter. More to the point, his eyelids were so weak that his attendants had to hold his eyes open in order for him to see. The chief had both generalized weakness and ptosis.

In the nineteenth and early twentieth centuries, clinical literature exploded with descriptions of patients with various neurological maladies. Most of the diseases we see and diagnose today were first described in the hundred years following James Parkinson's 1817 essay on the disease that now bears his name. Many clinical tales of patients with fluctuating paralysis were reported. They presented a major challenge to nineteenth-century neurologists and pathologists. The patients were weak, but their weakness came and went. Their muscles were rarely atrophied. That meant that the messages got through often enough to prevent atrophy. When the patients died, examination of their brains revealed nothing out of the ordinary. That was a problem. If the muscles were still there to respond, then it had to be the nervous system that was at fault. It could no

longer generate its orders, just as it couldn't in polio or amyotrophic lateral sclerosis.

Even the great Charcot could not figure out this disease. In 1892 Charcot described the case of a sixty-year-old medical inspector whom he had seen two years earlier. The patient had complained of diplopia and bilateral ptosis, but said all these symptoms disappeared after sleep (rather reminiscent of my patient). Weakness of the fingers and arms followed later. Charcot noted the fluctuation of the ptosis and also noted weakness in chewing. He made the diagnosis of polioencephalitis.

But polio does not fluctuate. Sleep is of no avail with polio. The muscles that are weak stay weak even after a very good night's sleep. More than that, the muscles, deprived of acetylcholine input to the receptors, become wasted and atrophied. Sleepy Jameson would have been misdiagnosed by Jean Martin Charcot. It is very humbling to read these clinical notes by one of the greatest neurologists and clinicians in the history of medicine, and wonder what future generations will make of my diagnoses. For one, I will be quite pleased if my clinical batting average is in the same league as Charcot's, even with the advantage of all our technical advances.

In 1895, three years later, a German neurologist named Jolly solved part of the riddle in the same publication in which he gave the disease its name. He used electrical current to stimulate the motor nerve and cause a muscle contraction in a patient with myasthenia gravis. The muscle contracted. That meant that the nerve responded normally to an electrical impulse and so did the muscle. No wonder the nervous system looked normal and there was no atrophy of the muscles. But things didn't remain normal. After repeated stimulations, a normal muscle keeps on contracting. But not in myasthenia gravis. Here, continuous electrical impulses lead to a weaker and weaker response. The longer Jolly stimulated the nerve, the weaker the response became. It was as if exercise caused weakness, which, of course, was just what happened clinically to patients like the one Jolly had studied.

The first impulse releases acetylcholine and the muscle responds as it should. But the neuromuscular junction is not normal, it can't recover normally, and its lack of recovery results in less response the next time and successively less with each stimulus—until late in the game two balls go flying over outstretched hands that just can't reach as high as they could a mere two hours earlier.

Myasthenia gravis also has one other unique characteristic as a disease. It is the only disease that is defined by its response to a drug. This characteristic became well defined in the years leading up to World War II and goes back to the nature of the neuromuscular junction defect.

The initial breakthrough in our understanding of this disorder came when Mary Walker, a resident in St. Alfege's Hospital, near London, had the idea that it would be worthwhile to try to use physostigmine, "a partial antidote to curare," on a patient with myasthenia gravis "in the hope that it would counteract the effect of the unknown substance which might be exerting a curare-like effect on the myoneural junctions." It seems that an American neurologist, Derek Denny-Brown, had visited London that year, had lectured on myasthenia gravis, and had discussed the resemblance between myasthenia and curare poisoning. Physostigmine (or eserine) was known to act as an antidote to curare. Denny-Brown was one of the most respected neurologists of his generation, an insightful clinician and inventive researcher. He understood the relationship between myasthenia and curare. It never occurred to him to give physostigmine to a myasthenic. There was no "eureka" for him.

Mary Walker remembered Denny-Brown's comments the next time she saw a patient with myasthenia. If physostigmine worked in curare poisoning, it was worth a try in myasthenia. She gave her fifty-six-year-old patient an injection of physostigmine salicylate. The patient's weakness improved. Dr. Walker tried again with similar success. And yet again. The physostigmine worked. No one injection improved all of the patient's symptoms, and sometimes the injection failed to produce any

obvious benefit. But overall the benefit was clear. Controlled injections of a wide variety of other substances had no effect on the weakness.

The history of physostigmine is interesting. It is the active substance of the esere beans of Calabar, a district in what is now Nigeria and a center of slave trade in West Africa. The people who lived there had the custom of forcing anyone who was accused of witchcraft to undergo trial by poison. The poison they used was derived from poisonous seeds of the esere plant. Anyone suspected of witchcraft was given eight of the beans in water. The accused's mouth would shake and mucus would come from his nose if he were guilty. If he vomited, he was declared innocent. Both of these responses are pharmacological effects of esere, which became known as both eserine and physostigmine.

In another report Mary Walker reported the same improvement from a related medication called prostigmine, which could be taken orally. Walker's two reports, both published in the late 1930s, revolutionized our entire approach to myasthenia. This disease could now be diagnosed accurately and then treated successfully.

Physostigmine improves the weakness in myasthenia the same way that it reverses the blockade of the neuromuscular junction caused by curare. Physostigmine blocks acetylcholinesterase, the enzyme that destroys acetylcholine. Blockage of this enzyme increases the life of acetylcholine so more remains in the synaptic cleft. There is more opportunity for that acetylcholine to reach the partially blocked receptor, and once it does the receptor responds.

Acetylcholinesterase inhibitors quickly became the standard form of treatment of myasthenia and the gold standard for diagnosis of myasthenia. The diagnostic test now defines the disease. Injection of physostigmine or any other acetylcholinesterase inhibitor will reverse the weakness. Today these injections are done with a fast-acting analogue known as Tensilon. Such tests are so specific that myasthenia is often defined as muscular

weakness reversed by the use of an acetylcholinesterase inhibitor.

I was itching to give Dwight Jameson an injection of Tensilon but I had nothing to test. He was normal. I could detect no weakness on examining him. If there was no weakness, there would be nothing that Tensilon could improve.

According to Dwight's history, his weakness appeared with exercise. I told him to exercise. Our offices were on the ninth floor. I had Dwight run up and down the stairs. Once. Twice. Three times. I examined him after three round-trips. I thought I noted some ptosis, especially in the right eye. When I asked him to count from one to twenty, the last two or three numbers seemed to be slightly slurred. There was something there but not quite enough to study or test.

Back to the stairs. A fourth time. Then a fifth. He was getting tired and I was getting tired of waiting for him. By now he knew something was wrong. He was seeing double. He had severe ptosis bilaterally. His eyes did not track normally. By the time he counted back to twelve, he was slurring his words. "Twelfth, eff-lef-thens. . . ."

I gave him the Tensilon and waited, but didn't have to for very long. Less than a minute. Dwight's eyelids lifted up. The ptosis was gone. His eyes straightened out. They now moved in conjunction with each other. His speech became crystal clear. There was no slurring at all. Dwight Jameson had a positive Tensilon test. By our definition of the disease, Dwight Jameson, First-Half Jameson, Sleepy Jameson had myasthenia gravis.

I told him what was wrong. He asked me what I could do to help him. One option was the use of medications much like the Tensilon I had just given him. "That sure helped," he observed.

It clearly had helped him, but such medicines are not unmixed blessings. They themselves are toxins. That is why crisis management in myasthenia always seems to go wrong. No matter what decision you make, the odds are against you. Insufficient amounts of acetylcholine at the receptors cause weakness, but so does too much. The right amount is a narrow range that is hard to obtain and even harder to maintain.

"Isn't there anything elthes you can do?" he slurred. The Tensilon had worn off by then. He was again slurring his speech and looking very sleepy. His natural recovery would take more time.

Fortunately, there was more that could be done. The reason I had more to offer Sleepy Jameson, more than mere variants on the medications introduced by Mary Walker fifty years earlier, was that we now had a far better understanding of the disease. We now know why myasthenia is an immune disease. It is, in fact, an autoimmune disease. Autoimmune diseases are a group of disorders in which the patient produces antibodies against one or more proteins of his own body. If that antibody interacts with a normal antigen of the thyroid, a disease called Hashimoto's thyroiditis results. In myasthenia, the abnormal antibody reacts with the motor end plate, more specifically, with the protein of the acetylcholine receptor of the end plate. These antibodies can be measured in the bloodstream of patients with myasthenia gravis. The circulation of these antibodies is one of the reasons exercise causes weakness. Exercise causes more blood to be pumped to the active muscles. More blood means exposure to more antibodies. This creates more chances for antibodies to latch on to receptor site antigens and block the synapses; and more blockage means more weakness. Exercise also stresses the reserve capacity of the motor end plates.

I told Dwight that we would do a blood test to measure his level of acetylcholine receptor antibodies. He wanted more than just the results of some esoteric blood tests.

Does this antibody produce the disease? It seems to. If purified acetylcholine receptors from electric eels are injected into rabbits, the rabbits produce antibodies to these foreign antigens. These antibodies then react with the rabbit's own acetylcholine receptors. The rabbits also become weak. In fact, the disease in rabbits has so many clinical features in common with myasthenia gravis that it is called experimental autoimmune myasthenia gravis. These antibodies can be measured in the sera from these rabbits by the same method we used to measure them in

Dwight. The similarity of this antigen, from electric eels to humans, is impressive. It could almost make a person believe in evolution.

It seems that the basic defect in myasthenia gravis is caused by a loss of acetylcholine receptor protein from the postsynaptic membrane. The antibody-antigen reaction reduces the available number of receptors, and this causes the weakness that is so damn grave. But the reaction is not the cause of the disease. It is the mechanism by which the weakness occurs. But how does this entire process become triggered? Why would Dwight Jameson have suddenly started making antibodies to attack his own body?

The production of specific antibodies, like neuronal learning, could be the result of either instruction or selection—the same age-old question that has perplexed scientists and philosophers since at least the time of Socrates. The traditional scientific view has considered this to be a perfect example of instructive learning on the part of the immune system.

Immunologists have pointed out for years that the body is capable of manufacturing an antibody for almost any foreign substance, or antigen, introduced into the body. The huge number and variety of potential antigens and subsequent antigen-induced antibodies make the notion of instruction very attractive. This attractiveness had been furthered by the observation that the body also manufactures antibodies to artificial substances that have been newly synthesized and had never before existed in nature.

What process other than instruction could possibly explain this? Looks can, however, be very deceiving. The power of the process of selection should never be underestimated.

When a foreign substance enters the body, a preexisting cell immediately recognizes the intruder and, in order to defend the body from it, begins to multiply and manufacture a range of proteins—including within that range the one protein (antibody) that neutralizes the chemical intruder. As the preexisting cell multiplies, there can be minor mutations (genetic drift) that can, in turn, make other proteins that are even more effective against the intruder. What once looked like an instruction process, with

the body developing a new molecule in response to the environment, has turned out to be a selection process.

In this selection process the foreign element selects a preexisting cell within the body (or is selected by that cell) and that cell produces the range of antibodies that it can produce. No more and no less. This range of antibody responses wards off the intruding antigen. It is all a matter of selection.

Selection is nothing terribly new. In 1943, Nobel Prize winners Salvador Luria and Max Delbrück studied the problem of bacterial adaptation to antibiotics. They discovered that bacteria do not really adapt to the antibiotic in their environment. Entirely new strains of antibiotic-resistant bacteria do not spontaneously generate. The process is one of selection.

In this selection process, preexisting alternative forms of bacteria flourish, not entirely new bacteria. Most bacteria faced with the bacteriocidal environment died off. A few survived. Those that survived did so for a reason. Survival wasn't a random event. The bacteria had some capability that had allowed them to become the only bacteria still surviving in that environment. In effect, survival of those that were fittest to meet the challenge. The so-called adaptive enzymes that are responsible for today's explosion of antibiotic-resistant bacteria are produced by genes that were already present in a small number of bacteria. The problem has not been new bacteria so much as the widespread extension of the altered environment, so that those few that were resistant were given the opportunity to become the most fit and survive. Selection, not mutation or instruction.

Socrates may have been right after all. He taught that all learning was nothing more than being reminded of what was already in the brain. He never explained why learning often remains so darn difficult.

What does this process of selection have to do with First-Half Jameson? He possessed within his body the immune cells that were capable of producing antiacetylcholine receptor antibodies. Many of us probably do. Normally we don't produce that or any other antibody to our own antigens. Then in Dwight this cell was selected into action. But why? How?

Most likely the selection was spurred by some trivial, unrelated event. Perhaps it was a viral infection or some other foreign substance that somehow entered into the body and then selected the right cell to produce antibodies to its antigens, but the wrong cell as far as Dwight was concerned. That cell was selected into activity and produced a range of antibodies to a number of antigens. One of these antibodies was Dwight's own acetylcholine receptor protein. The result was the disease we call myasthenia gravis.

The overlap of this selection and response system is not always a bad thing. In fact, the overlap can be helpful. It explains why smallpox now survives only in a few laboratories around the world, even though during the sixteenth and seventeenth centuries one out of three Europeans who survived infancy died of the disease. Edward Jenner, an eighteenth-century British physician, realized that milkmaids who had had cowpox, a mild infection of the hands that was an occupational hazard of milkmaids, never developed smallpox. Jennerian vaccination consists of intentionally spreading cowpox in order to prevent smallpox. It works because the antibodies induced by the virus of cowpox also interact with the antigens on the smallpox virus. It has worked so well that smallpox has become a veritable "endangered species."

"Where do those antibodies come from?" Dwight asked me.

"The thymus gland," I replied.

That was the key to what we might do to help Dwight Jameson and perhaps even cure him. It had been known for years that the thymus gland may be enlarged in some patients with myasthenia. At times there can even be a tumor in the thymus, a thymoma. Such tumors, like all tumors, require treatment. As early as the 1930s, it was known that surgical removal of the thymus gland with its tumor was sometimes followed by improvement in the patient's myasthenia. Interest in thymectomy as a treatment for myasthenia stems from the observations of an English surgeon named Alfred Blaylock. In 1936, Blaylock removed a cystic thymic tumor from a young woman with progressively severe myasthenia gravis. This tumor had been

irradiated previously without effect on either the tumor or the myasthenia. Blaylock reported the beneficial effect of the operation three years later, when the patient's myasthenia was considerably improved. This documented success initiated the somewhat illogical decision to remove thymus glands without tumors from other myasthenics. It took almost forty years to realize how frequently this procedure helped the patients. By the time I saw Dwight, thymectomy had become a cornerstone in the treatment of myasthenia and was usually combined with the use of medications that decreased the production of antibodies, immune suppressors of various types.

"So what's the plan?" he persisted.

We measured his level of acetylcholine receptor antibodies. It was elevated. Just what we had expected. We did an MRI scan of his chest. His thymus gland was enlarged, another nonsurprise. After a couple of weeks of immunosuppressive treatment, a chest surgeon removed Dwight's thymus gland. Dwight stayed on immunosuppressant therapy until the next summer when training camp started.

Jameson went on to have a very good preseason, and he won back his job as free safety. He then had a good season, playing as well in the second half as he did in the first half. He was not an all-pro. He never had been. He did, however, play another four years and then became a defensive coach at the college where he'd been mentioned as a possible All-American candidate.

Dwight never lost the nickname Sleepy, but no one ever called him First-Half again. To this day his myasthenia has not recurred.

Not everyone who receives immunosuppressive therapy does as well as Dwight Jameson did. Our modern use of immunosuppression dates back to 1965 and a report by a group of Swedish physicians. They used the pituitary hormone that stimulates the adrenal gland, adrenocorticotrophic hormone (ACTH), or corticotrophin. It increases the production of steroids by the adrenal glands. These steroids, in turn, suppress immune responses. The Swedish group studied patients in severe myasthenic crises, often on respirators. After an initial

period of deterioration, the patients who had been given ACTH improved to the point where they no longer needed respiratory support. On average it took about ten days to go from being dependent on a ventilator to being free. That was progress. One of the patients in this report was identified by his initials, H.G.

H.G. was Hjalmar Gullberg, an outstanding Swedish poet and a member of the Swedish Academy. At the age of fifty-nine, H.G. developed myasthenia gravis. His condition deteriorated rapidly. Prostigmine treatment only temporarily restored his strength. The poet's myasthenia had struck him while he was working on a book of poems inspired by Dante. His illness gave the last poem in this collection an aura of imminent death. After a brief remission, a dramatic exacerbation followed. The poet became bedridden once again. A tracheostomy was performed and he was placed on artificial ventilation.

In the era before widespread thymectomy and aggressive immunosuppression, respiratory support was the key to preserving life. Even while on the respirator, Gullberg was able to write, and he began his last volume of poems, *Eyes, Lips*, a work that is intensely personal and moving.

He was given another course of corticotrophin, which resulted in a dramatic change in his condition. His friends regarded this latest remission as miraculous. He had apparently been brought back to life. But during the treatment that saved his life, he had been through three tracheostomies. The corticotrophin courses had added months to his life, but H.G. soon realized that the myasthenic symptoms were returning. He once again became unable to talk or swallow. He wrote to his friends that he would not go through a fourth tracheostomy or suffer through another ordeal on a respirator. He preferred to die. The next morning, he walked down to a lake near his home. One of the poems he had written in his youth became his epitaph:

there is a lake
thereafter—nothing more.