

## Case Records of the Massachusetts General Hospital



## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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## Case 22-1997

## PRESENTATION OF CASE

A 58-year-old right-handed woman was admitted to the hospital because of multiple cranial neuropathies.

The patient had been well until two days earlier, when she began to have difficulty swallowing food while having dinner at home. During the next two or three hours, diplopia developed, with marked dysarthria to the point of losing the power of speech. She was taken to another hospital, where attempted magnetic resonance imaging (MRI) and angiographic studies could not be performed because of her inability to cooperate. Approximately 24 hours after her admission there, her condition was unimproved, and she was transferred to this hospital.

The patient was a housewife. She had adult-onset diabetes mellitus, which was controlled by diet. There was no history of previous weakness, exposure to ticks, abdominal pain, cancer, or recent travel and no family history of neuromuscular disorders. The meal she had been eating when her symptoms developed did not include home-canned foods, pork, or vegetables, and the food was shared by her husband, who remained well.

On arrival in the emergency ward, the patient was unable to speak but could nod and shake her head, mouth and write words, and give appropriate responses to queries and commands. The forced vital capacity was 600 ml. Tracheal intubation was performed, with the institution of mechanical ventilation. An edrophonium chloride test was negative. The patient was admitted to an intensive care unit.

The temperature was 37.2°C, the pulse was 76, and the respirations were mechanically controlled, with intermittent mandatory ventilation at a rate of 8 breaths per minute. The blood pressure was 140/85 mm Hg.

The physical examination was normal except for

obesity. On neurologic examination, the patient was alert and fully oriented. The visual fields were full. Bilateral ptosis was present; the pupils were 4 mm in diameter and reactive. There was weakness of abduction, especially on the left side. Almost no upward gaze was present, and attempts at upward gaze were marked by adduction of the left eye; convergence was preserved. Facial sensation was intact on testing with light touch and pinprick. Bifacial weakness was present. The palate was symmetric, and the gag reflex was active in response to manipulation of the nasotracheal tube. The tongue was weak. The patient was able to move her arms and legs. Muscle bulk and tone were normal, and proximal strength was 4+/5 in her arms and legs, with a distal strength of 5/5. Finger and toe movements were rapid and symmetric. Sensation was intact on testing with light touch, pinprick, and vibration. There was slight dysmetria in the left arm on finger-to-nose testing. The deep-tendon reflexes were absent in the arms and ankles, the knee jerks were + bilaterally, and the plantar responses were flexor. No anal wink was elicited.

TABLE 1. HEMATOLOGIC LABORATORY VALUES.

VARIABLE	ON ADMISSION	ON FOURTH HOSPITAL DAY
Hematocrit (%)	48.3	37.7
White-cell count (per mm <sup>3</sup> )	10,600	4,000
Erythrocyte sedimentation rate (mm/hr)	8	
Differential count (%)		
Neutrophils	84	
Lymphocytes	15	
Monocytes	1	
Platelet count (per mm <sup>3</sup> )	152,000	80,000
Prothrombin time	Normal	
Partial-thromboplastin time	Normal	

TABLE 2. BLOOD CHEMICAL FINDINGS.

VARIABLE	VALUE
Sodium (mmol/liter)	141
Potassium (mmol/liter)	3.9
Chloride (mmol/liter)	110
Carbon dioxide (mmol/liter)	22.5
Glucose (mg/dl)*	165

\*To convert the value for glucose to millimoles per liter, multiply by 0.05551.



**Figure 1.** Anteroposterior Radiograph of the Chest Showing Low Lung Volumes and a Small Left Pleural Effusion.



**Figure 2.** Gadolinium-Enhanced T<sub>1</sub>-Weighted Axial MRI Scan at the Level of the Midbrain, Showing a Normal Brain Stem without Abnormal Enhancement of Cranial Nerves.

The urine was positive (+) for glucose and ketones; the sediment contained 8 red cells per high-power field. The urea nitrogen, creatinine, calcium, phosphorus, bilirubin, uric acid, total protein, albumin, globulin, lactate dehydrogenase, magnesium, aspartate aminotransferase, and alkaline phosphatase levels were normal. The results of other laboratory tests are shown in Tables 1 and 2. An electrocardiogram was normal. A radiograph of the chest (Fig. 1) showed low lung volumes, with crowding of the basilar lung markings, and a small left pleural effusion. The heart appeared normal. An MRI scan of the brain (Fig. 2), obtained before and after the administration of gadolinium, was normal except for a bright signal in the left maxillary sinus on T<sub>2</sub>-weighted images. A lumbar puncture was performed. The albumin and IgG levels were normal, no oligoclonal bands were detected, and staining and cultures for organisms, including acid-fast organisms and fungi, were negative. Other cerebrospinal fluid findings are shown in Table 3.

Mechanical ventilation was continued. Treatment with minidose heparin was begun, and cimetidine and trimethoprim-sulfamethoxazole were given intravenously. A nasogastric tube was inserted, and formula feedings were administered. The temperature rose daily to 38.2°C but was normal on most occasions. On the second hospital day, plasmapheresis was begun. On the third day, the ophthalmoplegia was more prominent. On the fourth day, there was complete areflexia, except for a + right knee jerk. The results of immunoelectrophoresis were normal, and tests for syphilis, rheumatoid factor, antinuclear antibodies, antibodies to *Borrelia burgdorferi*, and antineutrophil cytoplasmic antibodies were negative. The results of other laboratory tests are shown in Table 1.

Motor-nerve conduction studies of the left median, ulnar, and tibial nerves showed compound muscle action potentials that were uniformly low in amplitude and well synchronized. The distal motor latencies and conduction velocities were normal; the F responses were unidentifiable. The left sural and ulnar sensory-nerve action potentials were normal. The blink reflex was unobtainable on either side. Needle electromyographic examination showed no spontaneous activity in any of the muscles examined. The recruitment pattern was full in most muscles.

A diagnostic procedure was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. MICHAEL T. HAYES\*: May we review the radiologic findings?

DR. MICHAEL H. LEV: The chest film obtained on admission shows low lung volumes with basilar atelectasis and a small left pleural effusion (Fig. 1).

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**TABLE 3.** FINDINGS ON LUMBAR PUNCTURE.

VARIABLE	FINDING
Appearance of fluid	Clear, colorless
Malignant-tumor cells	Absent
Glucose (mg/dl)*	98
Protein (mg/dl)	28

\*To convert the value for glucose to millimoles per liter, multiply by 0.05551.

The gadolinium-enhanced cranial MRI scan (Fig. 2) reveals only a moderately bright signal in the left maxillary sinus on T<sub>2</sub>-weighted images; the cranial nerves, brain stem, cerebellum, cavernous-sinus region, and cerebral hemispheres appear normal.

DR. HAYES: The first step in determining the nature of this illness is to decide whether the process affected the central or peripheral nervous system. Processes that affect the brain stem acutely may cause multiple cranial-nerve palsies and quadriplegia without spasticity early in their course, with depressed or absent reflexes and loss of F responses on neurophysiologic evaluation.<sup>1</sup> In this case, the examination ruled out a central lesion by failing to reveal long-tract signs or a sensory deficit, which should have resulted from a lesion large enough to cause such widespread cranial-nerve and general motor dysfunction. The low-amplitude compound muscle action potentials demonstrated on nerve-conduction studies also clearly indicate that this illness originated in the peripheral nervous system.

In patients with widespread motor dysfunction, three broad categories of illness merit consideration: myopathy, motor neuropathy, and processes affecting the neuromuscular junction. Few myopathies are characterized by the rapidly progressive weakness and severe bulbar and respiratory compromise evident in this patient. Polymyositis is usually insidious and only rarely fulminant. Proximal-limb weakness and facial weakness are common manifestations, and dysphagia occurs in more than 25 percent of cases.<sup>2</sup> Although muscle tenderness and cramping are common,<sup>3</sup> the absence of pain is not unusual. The deterioration in this patient, however, would be exceptional even for fulminant polymyositis. Also, although dysphagia is common in polymyositis, it is usually due to esophageal dysmotility,<sup>2</sup> not pharyngeal weakness. Ptosis is rare in polymyositis. The sedimentation rate is elevated in most cases, and the lactate dehydrogenase and aspartate aminotransferase levels are often elevated, whereas these values were normal in this case. Finally, fibrillations and positive sharp waves on electromyographic examination are hallmarks of polymyositis. Periodic paralysis, which includes a group of disorders that cause rapid and profound weakness, frequently with loss of reflexes, tends to occur in the first few decades of life. Involvement of the cranial nerves is infrequent, and involvement of ocular muscles is very rare.

Several types of motor neuropathy can develop quickly but are unlikely in this case. Porphyria can produce a rapidly progressive neuropathy<sup>4</sup> but is usually diagnosed early in life and characterized by severe abdominal pain. Cranial nerves are affected infrequently, and paresthesias are prominent. Ingestion of the fruit of the buckthorn shrub can cause a rapidly progressive, severe neuropathy,<sup>5</sup> with quadriplegia and facial and pharyngeal weakness, but the shrub is

found mainly in Texas and Mexico. The normal sensory potentials in this case are further evidence against neuropathy associated with buckthorn. Poisoning with massive doses of thallium can result in a severe, widespread polyneuropathy,<sup>6</sup> often associated with hypokalemia, which was not present in this case. Also, the absence of stomatitis, mental changes, visual loss, and painful paresthesias, which are seen with thallium poisoning, makes it a very unlikely diagnosis.

The North American wood tick, *Dermacentor andersoni*, and the common dog tick, *D. variabilis*, can cause generalized paralysis,<sup>7</sup> but it usually evolves less quickly than this patient's illness, and removal of the tick results in rapid recovery. Poliomyelitis can cause rapidly evolving weakness, but fever is almost always present, and pleocytosis is characteristic.<sup>8</sup>

Acute inflammatory demyelinating polyneuropathy (the Guillain-Barré syndrome) must be considered. Its annual incidence is estimated to be 0.6 to 4 cases per 100,000 population.<sup>9,10</sup> A predominantly bulbar pattern may be present, with oculomotor palsies and ptosis in 10 percent of patients,<sup>11,12</sup> and more than half of patients have facial weakness. Oropharyngeal and lingual weakness are also common. Respiratory failure severe enough to require mechanical ventilation is seen in about 40 percent of cases.<sup>13-16</sup> Very rapid deterioration, with severe weakness developing within hours, occasionally occurs. Thus, the clinical presentation of this patient and the subsequent course of her illness are consistent with the Guillain-Barré syndrome, and plasma exchange was doubtless instituted with this possibility in mind. A few clinical features of this case, however, make the Guillain-Barré syndrome unlikely. The cerebrospinal fluid protein level was not elevated, as it often is in this disorder. The protein level may be normal, however, particularly early in the course of the disease and especially in cases with primarily bulbar involvement. Also, paresthesias, which occur in a high percentage of patients with the Guillain-Barré syndrome,<sup>17</sup> were not present. More important, the forced vital capacity in this case was only 600 ml at a time when limb weakness was mild. Severe respiratory compromise does not occur in the Guillain-Barré syndrome in the absence of marked limb and trunk weakness. In a retrospective study performed at this institution, all the patients with a vital capacity under 1000 ml were unable to stand or lift their arms off the bed.<sup>18</sup>

Finally, the results of neurophysiologic testing rule out the Guillain-Barré syndrome and indeed all neuropathic processes. The nerve-conduction studies showed none of the typical findings of demyelination. One could argue that the low amplitude of compound muscle action potentials and absence of F responses reflected conduction block. For that interpretation to be valid, however, the conduction block would have to have been both very proximal and very distal along the course of the nerve. One

might also argue that the low-amplitude compound muscle action potentials reflected a motor axonopathy. Both these interpretations are inconsistent with the findings on needle electromyographic examination, which showed normal recruitment patterns. The recruitment pattern indicates whether a normal number of motor units are able to fire when a muscle is maximally contracted. In neuropathic disorders, whether demyelinating or axonal, the compound muscle action potential drops markedly when the number of motor units capable of firing diminishes. Thus, the recruitment pattern is reduced in cases of severe neuropathy, which brings me to the final category of disorders under consideration, those of the neuromuscular junction.

Weakness due to dysfunction at the neuromuscular junction is seen in the Lambert-Eaton syndrome,<sup>19</sup> but it progresses slowly, cranial-nerve involvement is usually not as conspicuous as in this case, and respiratory failure is rare. Hypermagnesemia and the administration of an aminoglycoside or a polymyxin can cause neuromuscular blockade,<sup>20-22</sup> but neither was a factor in this case.

Myasthenia gravis causes weakness because of a decrease in the number of functioning acetylcholine receptors on the postsynaptic membrane. The muscle fibers may not function well despite the release of a normal amount of acetylcholine into the synapse with depolarization of the motor nerve. Ptosis, paresis of extraocular muscles, facial weakness, pharyngeal weakness, and respiratory failure may all occur. However, the course of the illness tends to be insidious. Even when deterioration is rapid, it is usually not as precipitous as in this case. Reflexes are generally preserved until there is severe weakness of the limbs. The negative edrophonium chloride test in this case does not rule out myasthenia gravis but makes it an unlikely diagnosis. The low-amplitude compound muscle action potentials demonstrated on the nerve-conduction studies are also uncharacteristic of myasthenia gravis. Typically, the amplitudes are minimally decreased, if at all, on conventional nerve-conduction studies.<sup>23</sup>

Another, rarer cause of weakness at the level of the neuromuscular junction is botulism, caused by a toxin synthesized by *Clostridium botulinum*, a gram-positive rod. The name of the disease is derived from the Latin *botulus*, or sausage, referring to an outbreak of the disease in southern Germany in the 1700s in which a number of people died as a result of eating tainted sausage.<sup>24</sup> The toxin is produced as a single 150-kd polypeptide chain, which is cleaved into two chains, a 100-kd chain that is involved in neuron-specific binding and aids in the intracellular penetration of the toxin and a 50-kd chain that cleaves important molecules in neurotransmitter packaging. The toxin impedes the formation of functioning acetylcholine-laden vesicles, markedly reducing the amount of acetylcholine available for release when a motor neuron

is depolarized.<sup>25,26</sup> Thus, the defect is presynaptic, unlike that in myasthenia gravis. Eight serotypes of botulism toxin are now recognized (A, B, C1, C2, D, E, F, and G). The toxins cleave different proteins but affect the same step in vesicle formation, resulting in the same clinical syndrome.<sup>25</sup>

Most cases of botulism follow the ingestion of contaminated foods in which the toxin has already been produced and released. A less common source is a wound that becomes infected by the bacteria, which then release the toxin into the wound. In infants, *C. botulinum* can colonize the gut and produce the toxin, which is then absorbed through the gut. Symptoms of botulism usually develop one to three days after the consumption of contaminated food but can occur within a few hours, depending on the amount of toxin ingested.

Ophthalmoparesis, facial weakness, and bulbar palsy are the most common initial symptoms of the disease.<sup>27</sup> Despite pharyngeal weakness, a gag reflex is often preserved, as in this case. Dilatation of the pupils is common but may be absent, as in this patient; indeed, in one series, less than half the patients had dilated pupils.<sup>28</sup> Limb weakness and respiratory compromise may follow, although respiratory weakness can occur without severe limb weakness. Reflexes may be depressed or absent. Sensation and cognition are almost always preserved. Despite the absence of cognitive deficits, electroencephalographic studies may show slowing of theta and delta activity. Botulism may occur in clusters of people ingesting the same tainted food, but sporadic cases are not unusual. Blood tests are normal in patients with botulism. Conventional nerve-conduction studies show low-amplitude compound muscle action potentials and normal sensory conduction. Needle electromyographic examination may show fibrillation and sharp waves; motor units may be normal or myopathic, and recruitment patterns are generally normal.<sup>23</sup>

The diagnosis of botulism can be made by injecting a sample of the patient's serum or a preparation of tainted food into mice intraperitoneally. The test is positive if the mouse becomes paralyzed and dies. Polymerase-chain-reaction assays have been developed to detect the bacteria rapidly but are not yet in common use.<sup>29,30</sup> Their purpose thus far has been to detect the toxin-producing bacteria in food rather than the illness in the patient.

In this case, with a clinical picture consistent with botulism, the most helpful diagnostic approach would be to demonstrate the presence of a presynaptic neuromuscular-junction disorder by further neurophysiologic testing. The amount of acetylcholine released into the synaptic cleft at the neuromuscular junction is determined according to the amount of calcium released into the presynaptic terminal and the number of acetylcholine-laden vesicles available for re-

lease. The amount of calcium released depends on the rate at which the motor nerve fires.

Slow rates of repetitive firing of a nerve (2 to 5 Hz) do not change the concentration of calcium at the presynaptic terminal very much, and the repetitive firing that occurs in presynaptic disorders depletes the already low stores of acetylcholine, resulting in a decrease in the amplitudes of compound muscle action potentials. This decremental response is seen in presynaptic and postsynaptic disorders of the neuromuscular junction. High-frequency stimulation (20 to 50 Hz) or maximal voluntary contraction of the muscle for 30 to 60 seconds raises the concentration of calcium in the presynaptic terminal. In normal neuromuscular junctions and in those with postsynaptic disorders, there is no change in the compound muscle action potential, since more than enough acetylcholine is released to stimulate the postsynaptic membrane maximally without raising the calcium concentration. In presynaptic neuromuscular-junction disorders, the enhanced release of acetylcholine results in a greater compound muscle action potential after tetanic stimulation of the nerve or a brief period of maximal contraction. This post-tetanic potentiation of the compound muscle action potential often lasts for several minutes in patients with botulism. The finding is diagnostic of a presynaptic disorder of the neuromuscular junction. Thus, I believe that the diagnostic test in this case was either low-frequency repetitive stimulation that elicited a decremental response followed by tetanic stimulation or, more likely, a brief period of maximal voluntary exercise that resulted in an increased amplitude of the initially low-amplitude compound muscle action potential. Either finding in this clinical setting would establish the diagnosis of botulism.

With improvements in intensive care, the mortality rate among patients with botulism has declined to about 20 percent. Recovery is characterized by brisk axonal sprouting, with improvement occurring over a period of weeks to months if supportive care is provided early in the course of the disease.

DR. SHREYAS V. PATEL: Are particular foods associated with this disease?

DR. HAYES: In infants honey may be implicated, but in most adults ingestion of the small amount of *C. botulinum* that may be present in honey does not cause colonization in the gut. Most cases follow the ingestion of canned or bottled foods prepared commercially or at home that have not been sterilized properly.

DR. SAAD SHAFQAT: We considered botulism, but the patient's family told us that she had not consumed any home-canned foods and that all her meals had been shared with other family members. We favored the diagnosis of the Guillain-Barré syndrome — specifically, the variant first described by

C. Miller Fisher and characterized by the presence of abnormalities of eye movement.<sup>31</sup>

#### CLINICAL DIAGNOSIS

Guillain-Barré syndrome, Fisher variant.

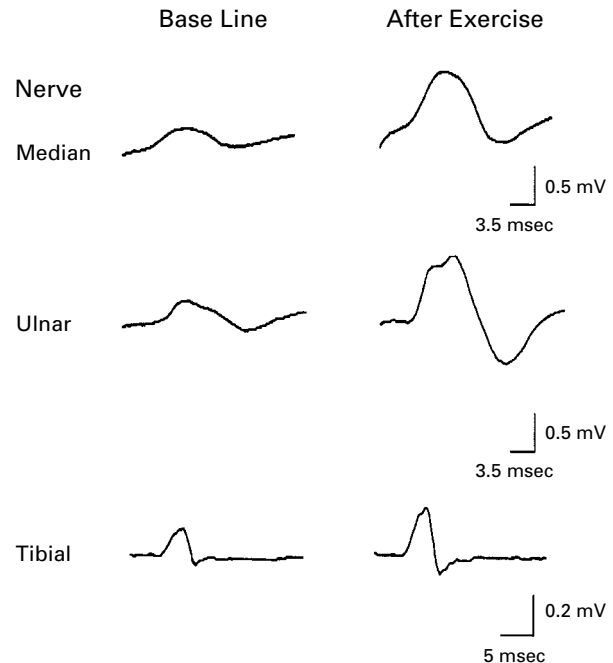
#### DR. MICHAEL T. HAYES'S DIAGNOSIS

Botulism.

#### PATHOLOGICAL DISCUSSION

DR. OSCAR SOTO: The diagnostic procedure was an electrophysiologic assessment of neuromuscular transmission. The amplitude and area of the compound muscle action potentials of the median, ulnar, and tibial nerves, recorded after 10 seconds of maximal voluntary contraction, were 187 to 286 percent of the basal responses (Fig. 3), with a return to base-line values within 1 minute (Fig. 4). Repetitive stimulation of the ulnar nerve at 3 Hz resulted in a 14 percent decrement in area and amplitude between the first and ninth responses; tetanic stimulation at 30 Hz for 1.5 seconds resulted in an incremental response of 170 percent in area and 280 percent in amplitude, indicating a degree of pseudofacilitation (Fig. 5).

The combination of low-amplitude compound



**Figure 3.** Post-Exercise Facilitation of the Median, Ulnar, and Tibial Compound Muscle Action Potentials.

The base-line median, ulnar, and tibial action potentials were obtained with distal stimulation. Immediately after exercise (10 seconds of maximal voluntary contraction), the action potentials show increases of 279, 286, and 187 percent in amplitude, respectively.

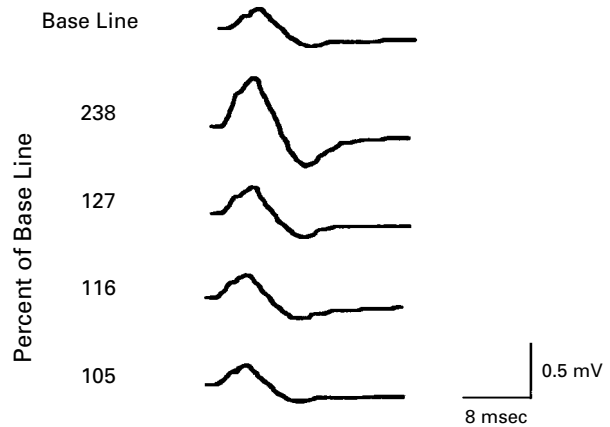
muscle action potentials, a decremental response to low rates of repetitive nerve stimulation, and an incremental response to high rates of stimulation or after a short period of maximal voluntary contraction is the hallmark of a presynaptic defect in neuromuscular transmission, which in this clinical setting was diagnostic of botulism.

The clostridial toxins target proteins that are involved in the priming of synaptic vesicles, making them sensitive to fast calcium-triggered exocytosis.<sup>32</sup> Decremental responses to repetitive stimulation at low rates are often absent, and there are typically incremental responses at high rates, but in severe cases, in which the presynaptic terminal is insensitive to calcium, the latter responses may also be absent.<sup>23,33,34</sup> Facilitation after exercise or tetanic stimulation is usually less pronounced in cases of botulism than in cases of the Lambert–Eaton myasthenic syndrome, and the response may persist for several minutes, although it did not in this case.<sup>35</sup> In addition to its effects on the presynaptic terminal, the toxin has been shown to convert the muscle acetylcholine receptor from the adult to the embryonic type, increasing the sensitivity of the muscle fibers to acetylcholine.<sup>36</sup> This alteration may be the basis for the frequent observation of fibrillation potentials in patients with botulism and in muscle injected with botulinum toxin for therapeutic purposes.

DR. KATHRYN L. RUOFF: The Microbiology Laboratory received serum and stool specimens for the detection of *C. botulinum* toxin. Most laboratories rely on the mouse neutralization test, a biologic assay, for toxin testing. Appropriate samples for testing include serum and stool specimens and also samples of any food that may have been ingested by the patient. In addition, efforts are made to isolate *C. botulinum* strains from stool specimens in the case of food-borne botulism. In the rare cases of botulism from a wound, samples of infected tissue are cultured.

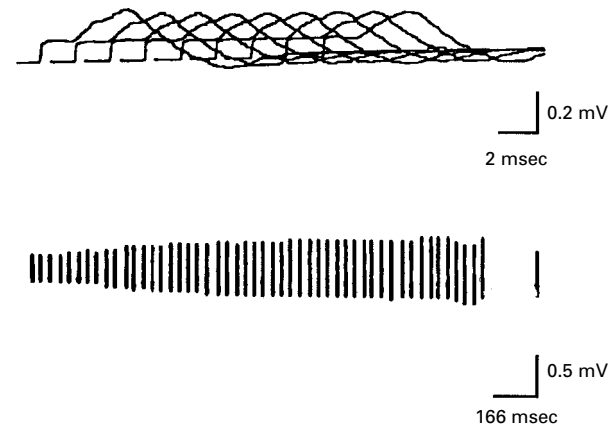
In this case, the mouse neutralization test was used to detect toxin in serum and an aqueous extract of stool. A specimen of stool was also tested for *C. botulinum* in an anaerobically incubated enrichment culture. Lipase-producing, gram-positive rods that were obligate anaerobes were presumptively identified as *C. botulinum*. The supernatants of broth cultures of these organisms were also tested for toxin.

In the biologic assay for toxin, in which the material being tested is injected intraperitoneally into mice, portions of the specimen that have been boiled to destroy the toxin or incubated with anti-toxin preparations to neutralize it are injected into mice as controls. This patient's serum was negative for *C. botulinum* toxin, which is not surprising, since only about 35 percent of patients with botulism have detectable toxin in their serum. The stool enrichment culture, however, was positive for *C. botulinum* type B toxin in the mouse neutralization



**Figure 4.** Progressive Decline in Facilitation of the Ulnar Nerve after Exercise, with a Return to Base-Line Values within One Minute.

Compound muscle action potentials were obtained at rest (base line), immediately after 10 seconds of maximal contraction, and at 15-second intervals thereafter.



**Figure 5.** Decremental Response to Slow-Rate Repetitive Stimulation (Top) and Incremental Response to Tetanic Stimulation at 30 Hz (Bottom).

test, and a strain identified as *C. botulinum* type B was isolated from the stool specimen.

DR. SHAFQAT: Once the presumptive diagnosis of the Guillain–Barré syndrome had been established, plasma exchange was instituted. On questioning the patient's family again, we learned that her husband had stored homemade, tomato-based spaghetti sauce in heat-sealed glass jars. Twenty-four hours before the onset of her symptoms, the patient had opened a jar and found it to be rancid but had tasted its contents before discarding it. No one else in the family was exposed to the spaghetti sauce. The discarded jar was later recovered by members of the Massachusetts Department of Public Health, and an anaerobic culture of the contents was positive for *C. botulinum*.

The patient's motor function gradually improved. Two weeks after admission, she was discharged to a rehabilitation facility. Oral intake was begun four weeks after the onset of her illness, and assisted ventilation was discontinued two weeks later. Two months after the onset of her symptoms, she was discharged home. Four months after the illness, she was walking with a cane and doing moderate housework.

DR. E. TESSA HEDLEY-WHYTE: Botulism was extremely rare in the United States until after World War I, when canned foods, prepared at home or commercially, became popular. Commercial canning was quickly recognized as a source of the disease and made safer by changing the processing methods. Nowadays, most cases of botulism are associated with the ingestion of home-canned foods. Because of the high acidity of tomatoes, they have not commonly been associated with botulism. However, many of the newer varieties of tomatoes have a low acid content, according to instruction books for home canning, which suggest adding lemon juice when canning tomatoes.

#### LABORATORY DIAGNOSIS

##### *Botulism.*

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