Correlation of Electrophysiology with Pathology, Pathogenesis, and Anticholinesterase Therapy in Post-Polio Syndrome[a]

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Aggressive vaccination programs may soon make acute paralytic poliomyelitis as rare worldwide as it is now in developed countries. However, the large cohort of individuals surviving paralytic poliomyelitis will continue to exist well into the next century. Currently, poliomyelitis is only second to stroke as a cause of paralysis in the United States, accounting for an estimated 640,000 individuals in the latest survey of the Centers for Disease Control.*[1]*

Although the first case of post-polio syndrome (PPS) was described as early as 1875,*[2,3]* it has only recently become clear how common this disorder is among individuals with prior poliomyelitis. Early surveys by Mary Codd and colleagues at the Mayo Clinic suggested that approximately 20% of subjects with antecedent polio developed new symptoms.*[4]* The wide array of new complaints reported by patients were grouped into a syndrome complex of new weakness, fatigue, and pain.*[4-7]* Current workers in the field now indicate that in excess of 50% of polio survivors are at risk for developing features of PPS,*[8]* and Munsat has suggested that 100% of polio survivors will develop at least some symptoms of the syndrome if followed for an adequate period.*[9]*

Is PPS a bona fide syndrome? In the clinical practice of caring for individuals with PPS symptoms, it is remarkable how often symptoms occur together, reminiscent of the Greek roots of syndrome, literally translated as "running together." There may be little to gain by splitting symptoms of PPS into subsyndromes within the symptom complex. For example, post-polio muscular atrophy (PPMA). which has been suggested as a distinct disease entity within the "late effects of polio," is not less likely to occur with pain as an unselected post-polio group.*[10]* Indeed, PPMA often occurs on a background of

longstanding fatigue and muscle pain, and thus may merely be a later manifestation of the disease process that can be designated PPS.*[10]*

What are the risks for developing PPS? Pioneering work by Halstead and colleagues suggested that severity of original paralytic poliomyelitis was a major risk factor,*[5]* a finding which has been confirmed by multiple investigators.*[11-14]* In addition, Halstead noted that patients were more likely to report symptoms with increasing time after polio.*[5]* In a 1987 study Jubelt and Cashman reviewed all reported cases of PPS and calculated that the mean time of PPS onset after paralytic poliomyelitis was 36 years.*[6]* Other possible risk factors include degree of recovery after polio*[15]* (which is logical in view of proposed mechanisms of PPS; see below), and muscle pain with exercise (which may be a marker for muscular overuse).*[14]*

What causes PPS? Many mechanisms have been proposed for this disorder, including the naturally occurring attrition of motor neurons with aging.*[14-16]* However, aging-related loss of motor neurons becomes prominent after age 60,*[17]* and the onset of PPS is most common 30-40 years after polio.*[6]* Perhaps the most compelling theory for the development of PPS was first introduced in a 1981 article in *Muscle & Nerve* by Wiechers and Hubble.*[18]* Loss of motor neurons in paralytic poliomyelitis induces compensatory axonal sprouting of remaining motor neurons, which markedly increases the number of muscle fibers innervated by the motor neuron. It is known that poliomyelitis is associated with extreme enlargement in the motor unit, reaching 7 or 8 times the normal innervation ratio of individual motor neurons.*[19]* The Wiechers-Hubble hypothesis avers that the prominent enlargement of motor units by axonal sprouting is not indefinitely stable and that enlarged units undergo progressive loss of terminal axonal sprouts with time after polio. This notion was based on data suggesting that single fiber EMG (SFEMG) jitter linearly increased with time after polio, which was taken as a measure of increasing instability of terminal axonal sprouts.*[18]* More recent data do not substantiate the finding of increasing jitter with time after polio.*[20,21]* However, the hypothesis that PPS represents a disorder of terminal axons has been supported by numerous investigators (see below).

LATE DENERVATION IN PATIENTS WITH PARALYTIC POLIOMYELITIS: A CONTROLLED STUDY

In the early 1980s, our group became interested in the diagnosis and treatment of individuals with PPS. At that time (as now), no objective test existed with which to distinguish PPS patients from stable subjects after polio, despite the important consequences of this disorder on activities of daily living, mobility, work, and disability status. We set out to develop diagnostic criteria based on objective laboratory assessment, including electromyography and muscle biopsy studies.*[22]* At that time, there was considerable controversy as to whether new denervation was detectable in PPS patients using these laboratory means, with a consensus agreeing that weakening patients could be distinguished by EMG studies from stable post-polio patients (reviewed in refs. 6 and 22). We recruited 13 PPS patients with well-established symptoms of new weakness and fatigue, and compared them with 5 post-polio control subjects who did not complain of new symptoms.*[22]* The two groups were carefully matched with regard to age, time after polio, and severity of the original illness. All patients were studied in a limb that had been historically involved with paralytic polio and exhibited weakness at the time of the study (no less than 3- on the Medical Research Council [MRC] scale). Patients suffering from PPS were studied in a limb reportedly affected by new PPS weakness.

Evaluations of all patients included a standardized history and physical examination, conventional electromyography, SFEMG, and muscle biopsy. Conventional nerve conduction studies were used to rule out neuropathy or radiculopathy, which might confound studies of muscle denervation. In addition, needle

EMG examination was performed in affected muscles, and evidence of denervation (fibrillations and positive waves) were recorded using a 5-point semiquantitative scale graded from - to + + + + +.

Single Fiber Electromyography

SFEMG was utilized in our controlled study to provide two objective measures of chronic and recent denervation.*[3]* *Fiber density* (FD), which reflects the number of muscle fibers innervated by the same motor neuron within the receptive volume of the SFEMG needle, was used to indicate the severity of original poliomyelitis. Normally, muscle fibers innervated by one motor neuron are widely distributed in a muscle, and only one or two muscle fiber potentials are detectable within the small receptive volume of the SFEMG needle. In polio subjects, increased fiber density is observed because of motor axonal sprouting in compensation for loss of neighboring motor axons. Thus, severity of original denervation should be correlated with increased SFEMG fiber density. We also adjusted the mean fiber density to muscle studied, generating a normalized "fiber density index" (FDI),*[22]* defined by the formula:

$$FDI = \frac{FD_{observed} - FD_{normal}}{FD_{normal}}$$

The use of the FDI allowed ready comparison of fiber density between muscle groups that had different normal fiber densities. FDI is 0 in a normal muscle and increases to >1.0 in a severely denervated muscle.

The second SFEMG parameter that was quantified and compared objectively between patient groups was *jitter*.*[22]* Jitter can reflect instability of terminal axonal conduction, neuromuscular junction transmission, and/or propagation of the action potentials over a muscle fiber.*[23]* In normal muscle, the depolarizations of two muscle fiber potentials innervated by the same motor neuron are essentially time locked; repetitive activation displays little variability of the time difference between the two potentials. In motor units that have been recently reinnervated following denervation, immaturity of terminal sprouts gives rise to increased variability of impulse conduction or neuromuscular junction transmission (jitter), or even failure of conduction/transmission (blocking), which will decrease in time after the insult over a course of months to a year or more.*[24]* Thus, increased SFEMG jitter in polio subjects can be regarded as an indicator of recent denervation and reinnervation.

Muscle Biopsy

Muscle biopsy was obtained from the same muscles studied with conventional EMG and SFEMG in order to more effectively correlate observations. Fiber type grouping and nuclear bags were taken as evidence of remote denervation, that is, severity of remote poliomyelitis. Fiber type grouping is due to the same mechanism that results in increased fiber density.*[25]* A normal muscle is a "mosaic" of fiber types recognized by histochemical staining for metabolic properties. As fiber type is determined by axonal influences, local reinnervating axonal sprouts after polio progressive atrophy, which years later presents in the muscle biopsy as a "nuclear bag" -- a fiber that has lost all its cytoplasm.*[25]*

Evidence of ongoing denervation was also sought in muscle biopsies, including atrophic angulated fibers, isolated or in groups.*[25]* A fiber that had been denervated weeks to months prior to the biopsy will be intermediate in size between normal and nuclear bag, and can be recognized as a small angulated fiber. When the recent denervation causing atrophic angulated fibers occurs in a distal axon or sprout, the atrophic fiber will be isolated from other atrophic fibers. In an extensively reinnervated muscle, death of a motor neuron or proximal degeneration of an extensively ramified axon induces simultaneous onset of

atrophy in a local group of muscle fibers, giving rise to grouped atrophy recognizable on muscle biopsy sections.

We also applied a novel technique for determining early denervation in human muscle biopsy sections, based upon muscle fiber expression of neural cell adhesion molecule (N-CAM).*[22,26,27]* Muscle N-CAM immunoreactivity, normally confined to satellite cells, end plates, intramuscular nerves, and some other regions, becomes diffusely expressed in a muscle fiber following denervation.*[26,27]* (N-CAM is also expressed in muscle fiber regeneration,*[27]* which can be readily distinguished from denervation by morphologic criteria and conventional staining.) Muscle fiber N-CAM provides a novel "window" into the pathophysiology of denervating diseases. Increased N-CAM immunoreactivity occurs very early in denervation, (as early as 2 days after experimental denervation of rat muscle*[26]*), whereas conventional criteria of denervation, such as fiber atrophy, manifest later. N-CAM immunoreactivity in a normal-sized myofiber can detect transiently denervated fibers destined to be reinnervated, as well as fibers destined to become progressively atrophic due to lack of successful reinnervation. Thus, N-CAM positivity in normal-sized versus small angulated fibers in polio patients may provide a morphologic correlate of ongoing motor unit remodeling (denervation-reinnervation) versus "permanent" denervation. In addition, N-CAM expression has been observed in rat muscle paralyzed by proximal nerve treatment with tetrodotoxin,*[26]* suggesting that suppression of N-CAM in normal muscle may be dependent upon effective activation by motor axons, even when the axon is structurally intact.

Results

Conventional EMG studies of 13 PPS patients and 5 post-polio controls revealed evidence of ongoing denervation (fibrillations and positive waves) in approximately one-half of all subjects studied, regardless of disease status (TABLE 1). SFEMG fiber density analysis demonstrated similar severity of paralytic poliomyelitis in patients and controls, as assessed by FDI (TABLE 1). Increased SFEMG jitter, taken as evidence of recent reinnervation or ongoing denervation, was increased in both groups to a similar degree, as was blocking (severe conduction/transmission abnormality resulting in intermittent failure of myofiber activation) (TABLE 1). No statistically significant difference was found between patients and controls with regard to evidence of ongoing denervation by conventional EMG or SFEMG.

TABLE 1. Electromyography Results.

	Control (n = 5)	Subjects with PPS (n = 13)
Conventional needle EMG		
Spontaneous activity	4/5	8/13
Single-Fiber EMG		
Fiber density	2.54 (1.95-3.04)	2.91 (1.58-5.07)
Fiber density index[a]	0.68 (0.24-1.04)	0.83 (0.02-2.23)
Mean jitter	73.7 (39.4-120.6)	77.4 (29.0-181.7)

	% Pairs abnormal jitter	65.3 (16.7-100.0)	44.3 (0-83.0)
	% Blocking	14.5 (0-50.0)	21.1 (0-70.0)

[a] $FDI = \frac{FD_{observed} - FD_{normal}}{FD_{normal}}$

Muscle biopsy studies demonstrated similar degrees of old denervation from original poliomyelitis, as assessed by fiber type grouping and quantification of nuclear bags (TABLE 2). Muscle fiber N-CAM immunoreactivity was observed in normal-sized muscle fibers (suggesting very active motor unit remodeling) in both subject groups to a similar degree (TABLE 2). Atrophic angulated fibers, isolated and in groups, were also observed in both patients groups, suggesting ongoing "permanent" denervation (TABLE 2). Scattered atrophy was observed in 14 of 16 post-polio biopsies, and grouped atrophy in 10 of 16. Again, using the semiquantitative scales of conventional muscle biopsy histochemistry or N-CAM positively, no statistically significant difference was observed between weakening PPS patients and stable post-polio controls.

TABLE 2. Muscle Biopsy Results.

Biopsy Findings	Control (n = 5)	Subjects with PPS (n = 13)
Type grouping	5/5	10/10
Nuclear bags	5/5	10/11
Fiber splitting	5/5	9/11
Scattered atrophy	5/5	9/11
Grouped atrophy	2/5	8/11
N-CAM$^+$ fibers	3.81% (0.6-12.0)	1.87% (0-5.5)

Abbreviation: N-CAM, neural cell adhesion molecule.

Our study design, in which electromyography and muscle biopsy were performed in the same muscle, enabled us to compare disparate forms of data*[22]* (FIG. 1). We found a significant correlation between increased jitter and fiber density, and a significant correlation between jitter and fiber type grouping (FIG. 2). Subsequent studies in collaboration with Maselli and colleagues also revealed a positive correlation of macro-EMG amplitudes (a measure of motor unit size*[30]* and possibly severity of original poliomyelitis) with jitter.*[28]* We also found that the presence of grouped atrophy was correlated with clinical muscle recovery after acute polio, nuclear bags, and type grouping, but was not associated with age.*[29]*

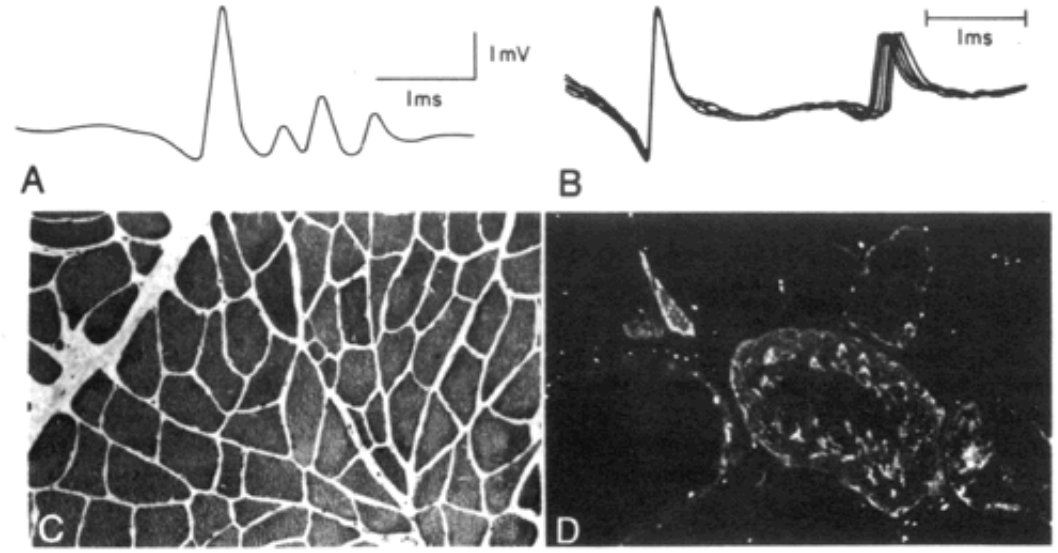

FIGURE 1. Single-fiber electromyographic studies (**A** and **B**) and muscle biopsy histopathologic studies (**C** and **D**) of the right deltoid muscle of an asymptomatic patient. The patient was a 64-year-old man who had had paralytic poliomyelitis involving all four limbs at the age of 9 and whose arms at the time of study had normal bulk and strength. **Panel A** shows four time-locked muscle-fiber action potentials observed in the determination of fiber density (mean ± SD normal value for age, 1.4 ± 0.11). **Panel B** shows 10 superimposed action-potential pairs indicating moderately increased jitter (mean consecutive difference, 74μs; normal for muscle, <35 μs). In **panel C**, a hematoxylin and eosin stain demonstrates fiber splitting (75x). **Panel D** shows neural-cell adhesion molecule immunoreactivity in small- and large-diameter muscle fibers (300x). (Cashman et al.*[22]* Reproduced with permission of the New England Journal of Medicine.)

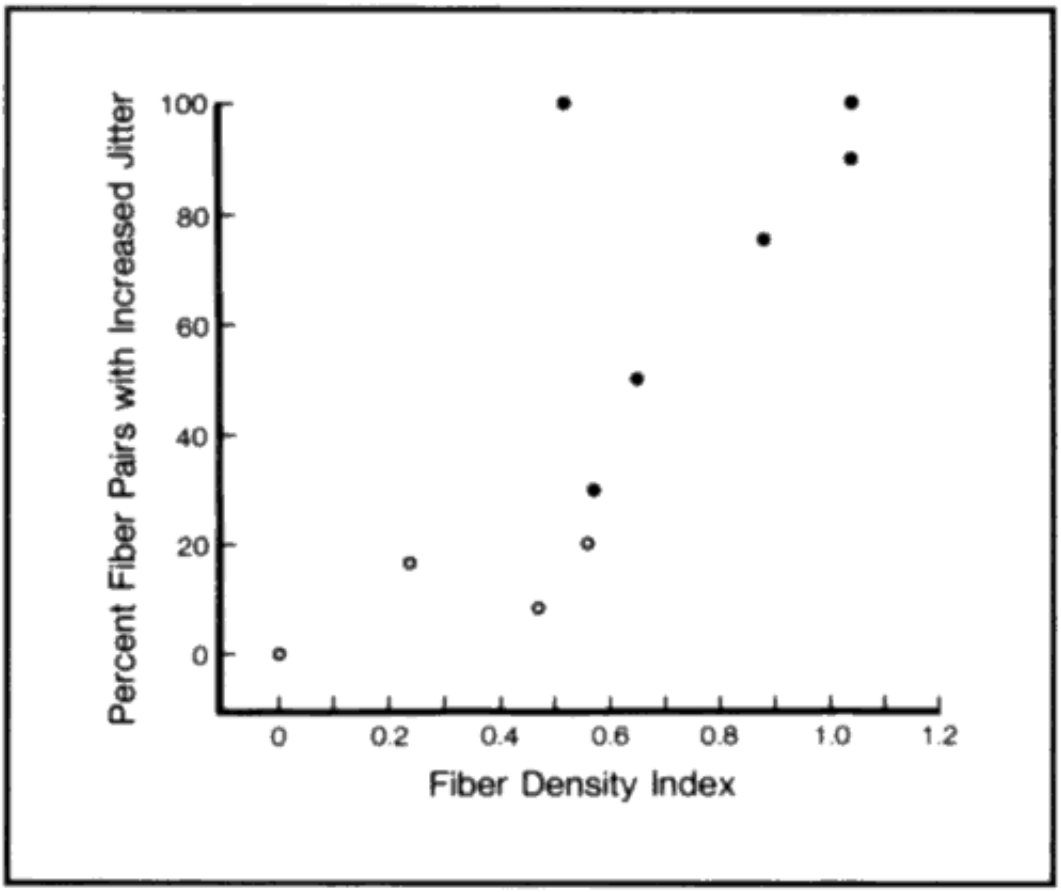

FIGURE 2. Percentages of fiber pairs exhibiting abnormal jitter according to the fiber-density index. The graph shows a correlation (Spearman r = 0.77, $p < 0.05$). Marked fiber type grouping (+ to + + + +) on biopsy (*filled circles*) was also associated with increased jitter (Wilcoxon rank sum $p < 0.01$). (Cashman et al.*[22]* Reproduced with permission of the New England Journal of Medicine.)

There were four conclusions to this work.*[22,29]* First, no EMG, SFEMG, or muscle biopsy feature could discriminate symptomatic from asymptomatic post-polio patients. Thus, using the best technology available, we were unable to provide a "diagnostic test" for PPS that would be useful to distinguish PPS patients from stable subjects after polio. Second, evidence of ongoing denervation, both motor unit remodeling and "permanent" denervation, was commonly observed in muscles of all patients with prior paralytic poliomyelitis. Aside from its significance regarding diagnosis of PPS, this conclusion suggested that the post-polio motor unit is an actively evolving, unstable entity. This supports the contention that clinical weakening occurs as a threshold phenomenon, and is not due to a pathophysiology unique to PPS. Third, evidence of ongoing denervation was strongly correlated with severity of remote denervation, suggesting that motor neurons most enlarged by previous polio are most likely to undergo late decompensation. This finding might be regarded as the laboratory correlate of the clinico-epidemiologic observation that the subjects with most severe polio are most likely to develop PPS.*[5,8-14]* Finally, proximal axon/motor neuron degeneration (as recognized by grouped atrophy in muscle biopsy) occurred most frequently in critically enlarged motor units of recovered poliomyelitis, and did not appear to be related to attrition of motor neurons with normal aging.

MOTOR UNIT SIZE IN POST-POLIO SYNDROME: A CONTROVERSY

Axonal sprouting can enlarge motor units to sevenfold normal units in recovery from paralytic poliomyelitis.*[19]* If the Wiechers-Hubble hypothesis is correct that PPS is due to terminal axonal degeneration,*[18]* one might expect that measures of motor unit size should show progressive diminution

in PPS. Local motor unit size can be estimated by direct quantification of axonal sprouting in motor point biopsy material,*[19]* but is most readily approached with macro-EMG, in which the size of a motor unit can be indirectly measured by a special EMG needle with a large receptive volume.*[30]* Despite some early encouraging results reported by Wiechers,*[31]* and then by Lange et al.,*[32]* we have been unable to demonstrate with this method a clear difference between weakening PPS patients and subjects with prior polio with no new weakness.*[28,33]* More recently, we have reasoned that a ratio of motor unit size (estimated by macro-EMG amplitude) to severity of remote denervation (estimated by fiber density on SFEMG) might reveal a net decrease of motor unit size in PPS patients controlled for severity of polio. Thus, a muscle affected by PPS might maintain its high fiber density while losing macro-EMG amplitude, and a stable muscle might maintain high fiber density with large macro-EMG amplitudes. However, we have found no statistically significant difference between the macro-EMG amplitude/fiber density ratio in a small group of PPS patients versus post-polio controls.*[33]*

THE NEUROMUSCULAR JUNCTION IN POST-POLIO SYNDROME

An additional area of interest for our group is the neuromuscular junction (NMJ) in PPS. PPS patients often provide a history consistent with NMJ dysfunction; muscle fatiguability is reported as a major symptom of the disorder (increased muscle weakness with exertion, resolving on rest) that is reminiscent of myasthenia gravis. In 1948, Hodes demonstrated a decrement of compound muscle action potential amplitude on repetitive stimulation studies in subjects with prior poliomyelitis, which partially reversed with intravenous neostigmine, an anticholinesterase agent.*[34]* Other groups, including our own, have reported increased SFEMG jitter and blocking in post-polio subjects, which could reflect neuromuscular junction transmission defects, as well as disordered terminal axonal conduction.*[11,18,22]* It is reasonable that a hugely enlarged axonal tree, such as that observed upon recovery from poliomyelitis, may be subject to critical limitations of distal components subserving NMJ transmission, such as acetylcholine vesicles. This hypothesis has received recent ultrastructural and electrophysiologic support from the work of Maselli and colleagues (this volume *[A]*).

Neuromuscular Junction Defects in High-Frequency Stimulation

Using stimulation-SFEMG,*[35]* we explored NMJ transmission in PPS and control subjects.*[36]* Stimulation-SFEMG allows the electromyographer to control rates of muscle fiber activation by nerve (which in conventional SFEMG is limited to the rate of voluntary activation), and permits the use of artificially high rates of stimulation to "stress" components of the distal axon and NMJ. In 1 out of 9 normal controls, SFEMG jitter significantly increased at higher rates of stimulation (10, 15, 20 Hz versus 1 and 5 Hz). However, in post-polio patients complaining of fatigue, approximately one-third (5/17) developed significantly increased jitter at high-frequency stimulation. Several presynaptic disorders have been described in which jitter increases with increased rates of stimulation.*[37-39]* A similar pattern of frequency dependence is observed in amyotrophic lateral sclerosis, where degenerating or grossly enlarged motor units may lack adequate acetylcholine release.*[40-42]* In presynaptic disorders in which jitter is reduced by high-frequency stimulation (such as Lambert-Eaton syndrome), the defect is thought to be associated with an abnormality of calcium influx at the nerve terminal.*[43]*

Notably, when PPS patients studied with stimulation-SFEMG were grouped into those showing increased jitter at high frequency stimulation and those showing no change with increased stimulation, clinical features such as age, sex, and severity of polio were not significantly different between the two groups.*[36]* However, there was a significant difference in time after polio between the two groups, with patients showing increased jitter on high-frequency stimulation more likely to be tested a longer time after acute illness (40 ± 7.6 versus 48.5 ± 6.0 years).*[36]* This suggests that the NMJ transmission defect is acquired

after polio, in a fashion consistent with the Wiechers-Hubble hypothesis of PPS.*[18]*

Acetylcholinesterase-responsive Neuromuscular Junction Defects

Do the NMJ defects observed in PPS have any practical implication for patient care? A possible insufficiency of acetylcholine release at the NMJ suggests that clinically applicable anticholinesterase agents may be useful in the management of fatigue and muscle fatigability, arguably the most disabling symptoms of the post-polio syndrome (see Trojan and Cashman, this volume *[B]*). We initially began open trials of the anticholinesterase pyridostigmine in a group of PPS patients complaining of fatigue.*[44-46]* Patients received "low dose" pyridostigmine, 120-180 mg/day. Response in this open trial was gratifying in that 64% of subjects had a subjective reduction in fatigue, as ascertained by the Hare scale of perceived exertion.*[47]* Interestingly, patients with most severe fatigue were most likely to have a therapeutic response to pyridostigmine.*[46]* Other groups have also reported some benefit of anticholinesterase agents in PPS.*[48,49]* Although low-dose pyridostigmine is well tolerated in a large series,*[50]* side effects of pyridostigmine, such as increased gut motility on initiation of dose, may unblind any controlled study, opening the possibility of placebo effect.

We have studied NMJ transmission with stimulation-SFEMG and intravenous edrophonium.*[51]* We find that approximately 50% of PPS patients develop a significant reduction in jitter after infusion of edrophonium 10 mg i.v. Patients were blinded to their electrophysiologic response and then were initiated on oral pyridostigmine. 60 mg t.i.d. After one month, 9 of a group of 17 reported a decrease in fatigue. Edrophonium response was significantly associated with fatigue reduction on oral pyridostigmine, and oral pyridostigmine response was significantly associated with a reduction in jitter on edrophonium infusion that followed the pharmacokinetics of this agent (FIG. 3; also see Trojan and Cashman, this volume *[B]*). This suggests that pyridostigmine response cannot he solely due to placebo effect, but may reflect an anticholinesterase-induced amelioration of NMJ transmission. Recent data also suggest that anticholinesterases may increase strength in PPS patients, possibly due to repair of NMJ transmission at synapses that are so unstable that they are subject to blocking of transmission.

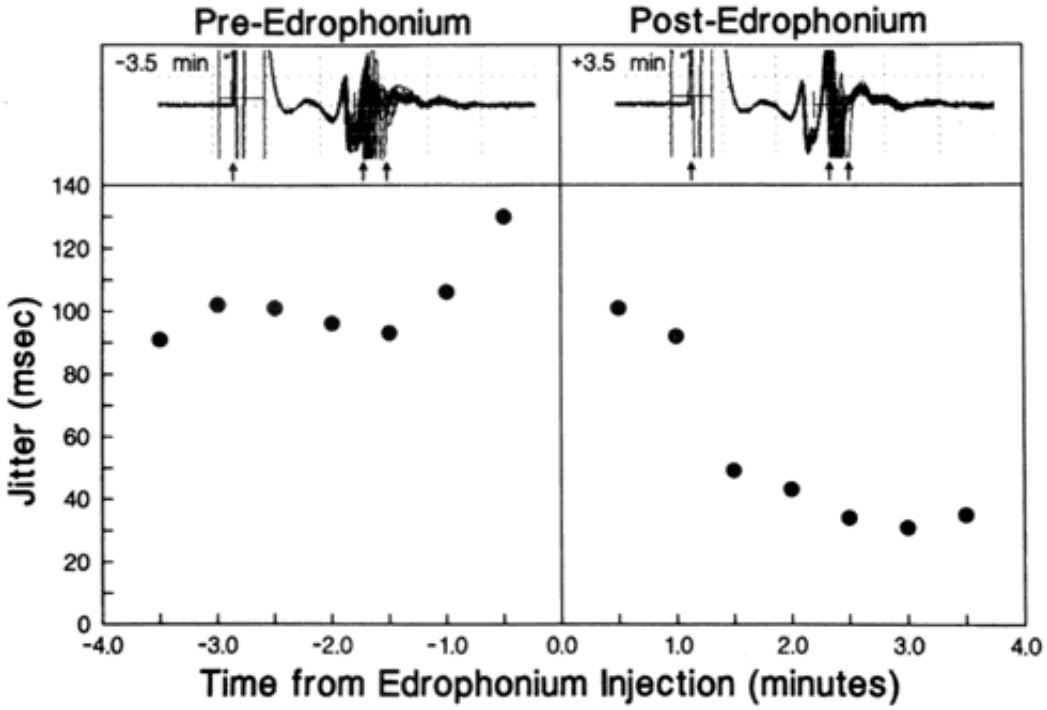

FIGURE 3. Pre- and post-edrophonium jitter as determined by stimulation-SFEMG in the vastus medialis muscle of a pyridostigmine responder. **Upper panels** show examples of raw data; the numerical jitter value is determined

by the mean consecutive difference between the stimulation artifact (*single arrow*) and the unstable potential (*double arrows*) in 50 superimposed stimulations. Jitter means (**lower panels**) were recorded every 30 s for 5 min before and 5 min after injection of edrophonium 10 mg (2 mg test dose followed by 8 mg 2 min after). Mean jitter for the 5 min before edrophonium (95.3 ± 5.09 μs SEM) significantly differed from mean jitter for the 5 min after edrophonium (47.6 ± 8.41 μs, $t = 4.65$, $p < 0.0001$). Thus, this subject was judged to have a significant reduction in jitter with edrophonium in the studied unstable potential. (Trojan *et al.*[51] Reproduced with permission of the *Journal of the Neurological Sciences*.)

CONCLUSIONS

A great deal of data has been generated on PPS, and a great deal more will be generated before we understand the pathophysiology of this common and disabling disorder. Perhaps now, to guide future work and direct therapeutic approaches, it is best to think of the symptoms of PPS as due to two lesions of the motor unit: a "progressive lesion" and a "fluctuating lesion." The progressive lesion gives rise to the symptom of slowly progressive weakness, and is due to the degeneration of terminal axons (and perhaps motor neurons) over the course of years. This lesion, best articulated by Wiechers and Hubble,[18] has been difficult to objectify because of its indolent nature. However, significant clinical weakening has indeed been quantified by several groups, including Munsat and colleagues,[7] and Sonies and Dalakas.[53] The best objective "proof" of the progressive lesion at present is the appearance of muscle fiber atrophy in biopsies, isolated and in groups, suggesting ongoing "permanent" denervation.[22] Diminution of motor unit size over time, as suggested by the macro-EMG studies of Lange *et al.*,[32] are also consistent with this hypothesis, albeit more controversial.

The other lesion of the PPS motor unit, hypothesized as a "fluctuating lesion," may be due to dysfunction of terminal axons, which gives rise to symptoms (muscle fatigability, generalized fatigue, and a component of weakness) that can change over the course of minutes to days. The underlying pathophysiology of these symptoms may be due to critical enlargement of motor units with limitations of distal components subserving axonal conduction and NMJ transmission, and/or the constant remodeling of the motor unit which appears to occur in virtually every individual after recovery from paralytic poliomyelitis. The best objective evidence for this ongoing lesion is provided by innumerable electrophysiologic studies demonstrating unstable motor unit action potentials and decrement on repetitive stimulation with conventional EMG, increased SFEMG jitter, and a host ofother studies.[54] In addition, the widespread expression of N-CAM in muscle biopsies of post-polio subjects (sometimes exceeding 10% of fibers)[22] strongly suggests that axono-myofiber interactions are distinctly unstable and/or immature. Clearly, agents that support the integrity or function of motor axonal sprouts may improve or delay patient symptoms in PPS.

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