Current Trends In

Post-poliomyelitis Syndrome

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International Polio Network, coordinated by Gazette International Networking Institute, advocates the dissemination of accurate information beneficial to the post-polio community. This collaboration with the Montreal Neurological Institute and Hospital assists in fulfilling that mission. For information about the additional work of the International Polio Network, contact International Polio Network, 4207 Lindell Boulevard, #110, Saint Louis, Missouri 63108 (314-534-0475; 314-534-5070 FAX; gini_intl@msn.com e–mail).

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Foreword

In 1948, when I was just one year old, too young to realize what was happening to me, I contracted paralytic poliomyelitis. Because of the development of the vaccines in the 1950s, poliomyelitis has not been on the minds of most North Americans since then—including mine. The only time I thought of it was during my annual trip before school to buy mismated saddle shoes.

When, in 1984, I heard the false rumor that people who had polio in the past were "getting polio again," I was stunned and disconcerted by the implications. In my search for accurate information to corroborate or refute that unconfirmed report, I found International Polio Network, an organization of which I am now the executive director.

Because there are consequences of living a life with the effects of acute poliomyelitis, International Polio Network provides current, critical information to the post-polio community. We recognize that:

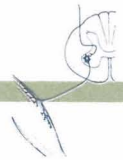
- Poliomyelitis affected each individual in a unique way, depending on the extent and location of the original paralysis.
- Polio survivors are experiencing new health-related problems, some of which are typical of the general aging population, but compounded by the original poliomyelitis.
- Many polio survivors are experiencing new problems that cannot be attributed to aging alone.

There are an estimated 640,000 paralytic polio survivors in the United States, tens of thousands in Canada, as well as thousands more around the world. Many of these survivors will seek medical attention, and it is imperative that health professionals be prepared to assist them.

International Polio Network is pleased to endorse "Current Trends in Post-poliomyelitis Syndrome," which provides clear and comprehensive information about the history, epidemiology, suspected pathophysiology, and management of the late effects of poliomyelitis. It is written from the combined perspective of two experts in the field, Dr. Daria A. Trojan, a specialist in physical medicine and rehabilitation, and Dr. Neil R. Cashman, a neurologist, both at the Montreal Neurological Institute and Hospital.

This monograph provides the foundation for meeting the needs of the post-polio population. To go a step further, contact International Polio Network.

Joan L. Headley
International Polio Network



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POST-POLIOMYELITIS SYNDROME

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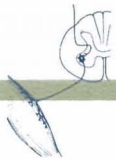


Chapter 1

Introduction: History and Description of Post-poliomyelitis Syndrome

Acute Paralytic Poliomyelitis

Acute paralytic poliomyelitis (APP) has likely been a part of human history since biblical times and may even date to eighteenth dynasty Egypt (1580-1350 BC). However, it was only in the nineteenth century that descriptions of APP epidemics began to appear.[1] Then, with the dramatic epidemics of the earlier part of the twentieth century, there was a large increase in cases. Following the introduction of the Salk vaccine in 1955 and the Sabin vaccine in 1961, the incidence of new cases dropped dramatically in the United States and Canada. However, APP is still a problem in less-developed parts of the world, and still occurs in developed countries as a rare complication of the oral poliovirus vaccine (OPV), or Sabin vaccine.

The polioviruses are small, RNA-containing viruses, classified in the genus Enterovirus within the family Picornaviridae. APP can be caused by three polioviruses (type 1, 2, or 3).[2] A person infected with one of the types is still at risk of infection from either of the two remaining types. Infection with the poliovirus occurs by the fecal/oral route. The virus replicates in the gastrointestinal tract, where it can penetrate the mucosa and be carried by blood throughout the body. It is excreted primarily in the stool, but also to a lesser degree in oropharyngeal secretions. After infection, and also after administration of the OPV, fecal secretion of the virus can continue for at least several weeks. Because of this, transmission to other persons can still occur easily in areas with poor sanitation and overcrowding.[2] In addition, inadequately vaccinated caretakers of children recently vaccinated with the OPV are at risk for becoming infected.

APP occurs as a result of motor neuron invasion by the poliovirus. Only 1% to 2% of infections result in neurologic symptoms and signs; the remaining infections are asymptomatic or produce only minor illness. APP can begin with symptoms characteristic of the minor illness, followed by high fever, headache, vomiting, neck and back stiffness, and paralysis.[2,3] Ninety percent to 95% of patients survive APP, and a majority of survivors experience at least some recovery of muscular function, usually in the first few months after infection.[3]

APP is primarily a disease of the motor unit. However, in fatal cases, lesions are also found in the cerebral cortex, primarily in the precentral gyrus, hypothalamus, thalamus, motor nuclei of the brainstem, reticular formation, vestibular nuclei, roof nuclei of the cerebellum,

and neurons in the intermediate columns.[3] During APP, motor neuron invasion may result in either motor neuron lysis or injury, with partial or complete recovery.[2] Motor neuron death causes denervation of muscle fibers, with resultant loss of voluntary activation of these fibers. If only a few motor neurons innervating a muscle are destroyed, no weakness may be perceived by the patient. Pathology studies have revealed that up to 20% of motor neurons may be destroyed in limbs with normal muscle function or only minimal paralysis.[4-6] A more severe loss of motor neurons may result in greater weakness or complete loss of muscle contraction.

Recovery of muscular force after APP can occur by collateral innervation through sprouting from remaining motor neurons or by muscle fiber hypertrophy of innervated muscle. Sprouting can produce reinnervation of locally denervated muscle fibers with restoration of the ability to produce a muscle contraction. Even with a loss of 50% of motor neurons supplying a muscle, the surviving motor neurons can achieve complete reinnervation, resulting in normal muscle strength.[7] Muscle biopsy studies have shown that the remaining motor neurons may innervate up to eight times the normal number of muscle fibers after recovery from APP.[8] In addition to motor neuron sprouting, muscle fiber hypertrophy can produce further recovery of muscular force after this illness.[9]

Recognition and Definition of Post-poliomyelitis Syndrome

Individuals who have recovered from APP may develop new difficulties later in life that are directly or indirectly related to the original motor neuron destruction by the poliovirus. The late onset of new weakness, fatigue, and atrophy in APP survivors, a condition now known as post-poliomyelitis syndrome (PPS), was first reported to the medical community in 1875 in Paris.[10,11] More than a century later, Wiechers and Hubbell[12] used single-fiber electromyography (SFEMG) and conventional EMG to study 10 stable post-polio patients and found evidence of diffuse neuromuscular junction (NMJ) transmission abnormalities and very large motor units even in normal or grade 4 (MRC scale) muscles. The concept of peripheral disintegration of the motor unit was proposed, and it was suggested that progressive weakness and fatigue may be much more widespread in patients with previous APP than first believed. Dalakas and coworkers[13] reported on a series of 27 post-polio patients followed for a mean of 8.2 years with muscle biopsy, CSF examinations, EMG, muscle strength evaluations, and other examinations. They confirmed the finding of evidence of NMJ defects, and also found signs of chronic and new denervation. An average 1% decline in muscle strength was noted. Cashman and colleagues[14,15] found clear evidence of active and ongoing denervation not only in newly weakened muscles but also in

clinically stable muscles in post-polio patients by EMG, SFEMG, muscle biopsy, and immunohistochemical analysis. Since then, the presence of widespread neuromuscular dysfunction has been confirmed by many investigators.

Mulder et al[16] first proposed criteria for the onset of new weakness manifesting many years after APP: (1) a credible history of APP, (2) partial recovery of function, (3) a minimum of 10 years of stabilization, and (4) the later development of progressive muscle weakness. They also suggested that there should be no other discernible causes of this increased weakness. Recently, Halstead[17] has proposed more specific criteria for PPS. These criteria include: (1) a previous episode of APP that is confirmed by history, physical exam, and EMG, (2) a period of neurologic recovery followed by a period of at least 20 years of neurologic and functional stability prior to onset of new problems, (3) the gradual or abrupt onset of new neurogenic weakness, which may or may not be accompanied by other problems such as excessive fatigue, muscle pain, joint pain, decreased endurance, decreased function, and atrophy, and (4) the exclusion of medical, orthopedic, and neurologic conditions that may be causing the new difficulties. He stressed that the new weakness should not be due to disuse of muscles, and that the individual should have "diminished function despite maintaining the usual level and intensity of activity."[18] A more practical definition of PPS might include all of the criteria proposed by Halstead[17] with the exception of EMG studies. (In our opinion, EMG studies should be reserved for those patients who have an unclear history of past APP, patients who may not have obvious signs of past APP on standard examination [weakness, atrophy, decreased reflexes], or those who may have other superimposed neurologic disease.)

Symptomatology of Post-poliomyelitis Syndrome

New weakness, fatigue, and pain are the three most common symptoms that may occur many years following APP; however, a wide variety of other symptoms may occur.[17,19-24] Fatigue is probably the major symptom of PPS, occurring in 59% to 89% of patients,[19,25] and is frequently cited as the most disabling symptom. Fatigue can be either general or muscular; often, both occur concurrently. General fatigue is usually described as a generalized exhaustion, similar to that which occurs with influenza. Typically, patients feel well rested in the morning but experience a progressive fatigue during the day, which usually worsens with physical activity.[26] Manifestations include an increased sleep requirement, naps or rest periods during the day, and decreased concentration. Muscular fatigue (or muscle fatiguability) is defined as increased weakness with exercise that improves with rest. It may be perceived by the patient as decreased

endurance. New weakness can occur in muscles previously involved or uninvolved at the time of APP; however, it occurs more frequently in muscles that were involved.[21] This phenomenon may be explained by the fact that previously "uninvolved" muscles may have had subclinical involvement at the time of APP. New weakness may be described as permanent or transient. Permanent new weakness is usually insidious in onset, but may also start suddenly, and is usually slowly progressive. Transient weakness is most likely muscular fatigue or decreased endurance.

Pain in PPS usually occurs in muscles or joints. Muscle pain is generally described as an aching or sore feeling that occurs after light physical activity, and frequently improves with rest.[21] Fibromyalgia is frequently present in a post-polio clinic, and may be another cause of muscle pain in these patients.[27] Joint pains may be chronic or intermittent, and are also usually aggravated by activity. They may be due to bursitis, tendinitis, or osteoarthritis from chronic overuse or abnormal use of weak, unstable limbs.

Other, less-frequently reported symptoms include new muscular atrophy, respiratory insufficiency from progressive muscular weakness, dysarthria, dysphagia, muscle cramps, cold intolerance, fasciculations, and new or progressive joint deformities.[21] New atrophy has been reported in 28% of patients in a post-polio clinic,[25] and may be a late phenomenon of PPS.[14] Muscle cramps are usually related to activity, and probably indicate overuse of muscles.

The new symptoms that occur as part of PPS may produce disabilities and handicaps for the patient involved. Mobility, especially stair-climbing, is most frequently affected. Dependence in basic activities of daily living is rare, but difficulties in instrumental activities of daily living (cooking, cleaning, shopping, driving) are more common.[28] Patients may also need new assistive devices, and may require a change or cessation of occupation.[19] Thus, new difficulties in a post-polio patient can produce a deterioration in function.

REFERENCES

1. Paul JR. *History of Poliomyelitis*. New Haven: Yale University Press; 1971:1-36.
2. Price RW, Plum F. Poliomyelitis. In: Vinken DJ, Bruyn GW, eds. *Handbook of Clinical Neurology* (vol. #34). Amsterdam: North Holland Biomedical Press, 1978:93-132.
3. Adams RD, Victor M. *Principles of Neurology*. New York: McGraw-Hill Book Company, 1993:641-644.
4. Bodian D, Howe HA. The pathology of early arrested and non-paralytic poliomyelitis. *Bull Johns Hopkins Hosp* 1941;69:135-147.
5. Bodian D. Poliomyelitis: pathologic anatomy. In: *Poliomyelitis* (papers and discussions presented at the First International Poliomyelitis Congress), Philadelphia: Lippincott, 1948:62-84,100-101.

6. Bodian D. The virus, the nerve cell and paralysis. A study of experimental poliomyelitis in the spinal cord. *Bull Johns Hopkins Hosp* 1948;83:1-107.

7. Sharrard WJW. Correlation between changes in the spinal cord and muscle paralysis in poliomyelitis: a preliminary report. *Proc R Soc Med* 1953;46:346-349.

8. Coers C, Woolf AL. Special pathology of the intramuscular nerves and nerve endings. In: *Innervation of Muscle. A Biopsy Study*. Springfield, IL: Charles C Thomas, 1959:64-66.

9. Borg K, Borg J, Edstrom L, Grimby L. Effects of excessive use of remaining muscle fibers in prior polio and LV lesion. *Muscle Nerve* 1988;11:1219-1230.

10. Cornel, Lepine. Sur en cas de paralysie général spinale antérieure subaigue, suivi d'autopsie. *Gax Méd Paris* 1875:127.

11. Raymond M. Paralysie essentialle de lénfance, atrophie musculaire consécutive. *Gaz Méd Paris* 1875-225.

12. Wiechers DO, Hubbell SL. Late changes in the motor unit after acute poliomyelitis. *Muscle Nerve* 1981;4:524-528.

13. Dalakas MC, Elder G, Hallett M, Ravits J, Baker M, Papadopoulos N, Albrecht P, Sever J. A long-term follow-up study of patients with post-poliomyelitis neuromuscular symptoms. *N Engl J Med* 1986;314:959-963.

14. Cashman NR, Maselli R, Wollmann R, Simon R, Heidkamp P, Antel JP. New muscle atrophy as a late symptom of the post-poliomyelitis syndrome. *Clin Ecol* 1987;5:11-13.

15. Cashman NR, Maselli R, Wollmann RL, Roos R, Simon R, Antel JP. Late denervation in patients with antecedent paralytic poliomyelitis. *N Engl J Med* 1987;317:7-12.

16. Mulder DW, Rosenbaum RA, Layton DD. Late progression of poliomyelitis or forme fruste amyotrophic lateral sclerosis? *Mayo Clin Proc* 1972;47:756-761.

17. Halstead LS. Post-polio syndrome: definition of an elusive concept. In: Munsat TL, ed. *Post-polio Syndrome*. Boston: Butterworth-Heinemann, 1991:23-38.

18. Gawne AC, Halstead LS. Post-polio syndrome: pathophysiology and clinical management. *Crit Rev Phys Rehab Med* 1995;7:147-188.

19. Codd MB, Mulder DW, Kurland LT, Beard CM, O'Fallon WM. Poliomyelitis in Rochester, Minnesota, 1935-1955: epidemiology and long-term sequelae. A preliminay report. In: Halstead LS, Wiechers DO, eds. *Late Effects of Poliomyelitis*. Miami, FL: Symposia Foundation, 1985:121-134.

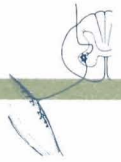
20. Halstead LS, Wiechers DO, Rossi CD. Late effects of poliomyelitis: a national survey. In: Halstead LS, Wiechers DO, eds. *Late Effects of Poliomyelitis*. Miami, FL: Symposia Foundation, 1985:11-31.

21. Jubelt B, Cashman NR. Neurological manifestations of the post-polio syndrome. *CRC Crit Rev Neurobiol* 1987;3:199-220.

22. Speier JL, Owen RR, Knapp M, Canine JK. Occurrence of post-polio sequelae in an epidemic population. In: Halstead LS, Wiechers DO, eds. *Research and Clinical Aspects of the Late Effects of Poliomyelitis*. White Plains, NY: March of Dimes Birth Defects Foundation, 1987:39-48.

23. Windebank AJ, Daube JR, Litchy WJ, Codd M, Chao EYS, Kurland LT, Iverson R. Late sequelae of paralytic poliomyelitis in Olmstead County, Minnesota. In: Halstead LS, Wiechers DO, eds. *Research and Clinical Aspects of the Late Effects of Poliomyelitis*. White Plains, NY: March of Dimes Birth Defects Foundation, 1987:27-38.

24. Windebank AJ, Litchy WJ, Daube JR, Kurland LT, Codd MB, Iverson R. Late effects of paralytic poliomyelitis in Olmsted County, Minnesota. *Neurology* 1991;41:501-507.

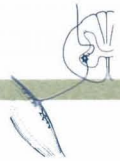


25. Halstead LS, Rossi CD. Post-polio syndrome: clinical experience with 132 consecutive outpatients. In: Halstead LS, Wiechers DO, eds. *Research and Clinical Aspects of the Late Effects of Poliomyelitis*. White Plains, NY: March of Dimes Birth Defects Foundation, 1987:13-26.

26. Berlly MH, Strauser WW, Hall KM. Fatigue in post-polio syndrome. *Arch Phys Med Rehab* 1991;72:115-118.

27. Trojan DA, Cashman NR. Fibromyalgia is common in a postpoliomyelitis clinic. *Arch Neurol* 1995;52:620-624.

28. Grimby G, Thoren Jonson AL. Disability in poliomyelitis sequelae. *Phys Ther* 1994;74:415-424.



Chapter 2

Epidemiologic Studies and Predictive Factors for Post-poliomyelitis Syndrome

Frequency of Poliomyelitis

Acute paralytic poliomyelitis (APP) is currently a rare disease in the United States and Canada. Since 1965, after widespread vaccination, its annual incidence has been less than 0.01 per 100,000 in the United States.[1] It now occurs as a rare complication of the Sabin live virus vaccine (1 case per 9.5 million doses of distributed vaccine in recipients, and 1 case per 3.2 million distributed doses in contacts of recipients).[2] An estimated 116,000 new cases of APP occurred worldwide in 1990.[3] More recently, because of a commitment by the World Health Organization to eradicate poliomyelitis by the year 2000,[3] the number of new cases worldwide dropped to only 6241 in 1994.[4]

Even though APP is uncommon in the United States and Canada, and is rapidly declining worldwide, a large group of polio survivors are still present. In 1987, the National Center for Health Statistics conducted the National Health Interview Survey and estimated that there were 640,000 survivors of APP in the United States.[5]

Frequency of Post-poliomyelitis Syndrome

Several population-based studies have attempted to identify the frequency of post-poliomyelitis syndrome (PPS) in individuals who have recovered from APP.[6-10] In the earliest study,[6] 201 cases of APP were identified between 1935 and 1955 in Olmsted County, Minnesota. Of the remaining 148 patients, follow-up information was obtained from 128 (86%) by a mailed questionnaire and telephone interview. Twenty-eight (22.4%) indicated a deterioration since their maximal functional recovery after APP. The most common new complaint was new joint pain (74%), followed by new weakness (71%) and increased fatigue (59%) (Table 1).

In Minneapolis, Minnesota, 1619 patients were hospitalized at three institutions.[7] Of the estimated 1542 survivors, 670 (43%) individuals were traced, and 327 (or 21% of survivors) completed a mailed questionnaire. New difficulties were reported by 41% of the respondents, with pain and cramping being the most frequently mentioned problem (47%), followed by decreased endurance (42%) and increased weakness (40%). Ramlow et al[10] identified 850 cases of acute paralytic and non-paralytic poliomyelitis for the period 1950 to 1955 in Allegheny

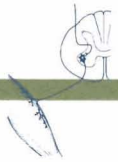


TABLE 1

POLIOMYELITIS LONG-TERM SEQUELAE IN 28 PATIENTS, ROCHESTER, MINNESOTA

New joint pain	74%
New weakness	71%
Increased fatigue	59%
New muscle cramp	51%
New muscle pain	48%
New muscle atrophy	46%
Increased sleep requirement	30%
New fasciculation	29%
New or increased deformity	25%
Decreased mobility	25%
Increased need for ambulatory aids	25%
Increased difficulty dressing	14%
Increased need for personal assistance	7%
Change/cessation of occupation	7%

From Codd et al.[6]

County, Pennsylvania. Twenty-two patients died in the acute phase of the illness, and 41 patients died later. Survey data were obtained with a validated mailed questionnaire from 551 (88%) of the 626 located survivors. The investigators found that 28.5% of paralytic cases had PPS (defined as "new weakness and muscle pain in the absence of an otherwise explanatory condition"); however, 38% of the 474 paralytic cases had new muscle weakness.

The studies completed thus far note a relatively high frequency of new difficulties, up to 64%, in individuals who had previously recovered from APP. However, the frequency of PPS (defined as new weakness many years after acute APP) is probably lower, between 20% and 40%.

Time of Onset of Post-poliomyelitis Syndrome

The natural history of the development of PPS is fairly characteristic in patients with past APP (Figure 1). APP is usually followed by a period of neurologic and functional recovery that can

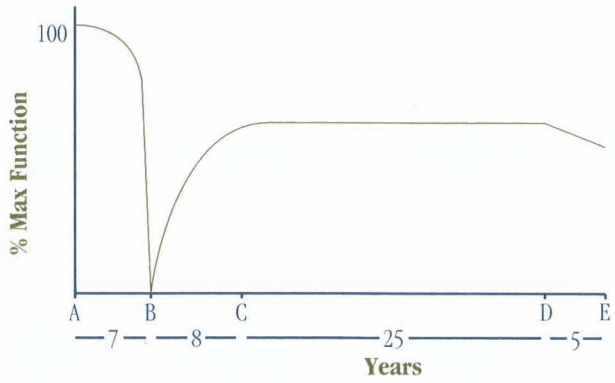
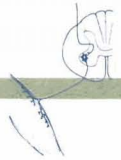


Figure 1. Natural history of poliomyelitis in a post-polio clinic. Functional changes at key milestones for 132 persons with post-poliomyelitis syndrome. Median times for this patient group are illustrated. A = birth; B = acute polio (7 years); C = maximum neurologic and functional recovery (B to C was 8 years); D = onset of new health problems (C to D was 25 years); E = time of evaluation (D to E was 5 years). Figure modified from Halstead and Rossi.[12] Reprinted with permission from March of Dimes Birth Defects Foundation and the authors.

occur over several months to years. Subsequent to this is a period of functional stability, usually lasting several decades. A review of several studies[11] has noted that the time range between the acute illness and the onset of new symptoms is 8 to 71 years, with the mean interval being approximately 35 years. Symptoms are more likely to occur earlier in those with more severe APP.[12] Therefore, PPS most commonly occurs 30 to 40 years after the initial illness.

Predictive Factors for Post-poliomyelitis Syndrome

Several studies have identified predictive factors for PPS.[8-10,12-14] Knowledge of predictive factors can help identify patients potentially at risk for acquiring PPS and, in the case of modifiable factors, can be used to help prevent the development of PPS. Predictive factors for PPS are a greater severity of initial APP,[8,9,12-14] a greater functional recovery after APP,[13] a more advanced age at APP,[12,13] a greater length of time since APP,[10,14] a lower disability level at presentation to clinic,[13] the presence of a permanent impairment after recovery from APP,[10] increased recent physical activity,[13] a greater age at time of presentation to clinic,[14] a recent weight gain,[14] muscle pain, especially



when associated with exercise,[14] and joint pain.[14] Ramlow et al[10] also found that female sex was a significant predictive factor; however, this finding has not been confirmed by other investigators.

The predictive factors identified are consistent with previously proposed hypotheses on the etiology of PPS. APP causes loss of motor neurons with associated weakness. Recovery of muscular strength can occur through terminal axonal sprouting, with reinnervation of denervated muscle fibers, and muscle fiber hypertrophy. PPS is believed to result from a distal degeneration of massively enlarged motor units, which occur as a result of this recovery process from APP.[15,16] Overuse[17,18] and the normal aging process[11,19] may be contributing factors.

Based on current knowledge of the pathophysiology of PPS, severity of APP as a measure of initial motor neuron destruction during the acute illness should be a risk factor for PPS. A greater severity of APP has been found to be a risk factor for PPS in a majority of studies.[8,9,12-14] A greater age at APP, which is known to correlate with severity of APP, has also been found to be a risk factor in two studies.[12,13] In contrast, Ramlow and coworkers[10] found that the presence of a permanent impairment after APP was a risk factor for PPS, and not the extent of initial paralysis. The authors concluded that this indicated PPS was determined by neuromuscular events that occurred during and shortly after the acute illness. The degree of initial motor unit enlargement after APP as measured by the degree of muscular recovery may be a risk factor for PPS. Klingman and coworkers[13] found that a greater functional recovery was a risk factor for PPS, and we found that a greater recovery occurred in PPS patients than APP controls.[14] However, this difference did not reach statistical significance.

Because overuse has been identified as a contributing factor for PPS, such factors as length of time since APP, joint and muscle pain, physical activity, and weight gain may be predictive factors for PPS. A greater length of time after APP was found to be a risk factor for PPS in two studies,[10,14] but not in another study.[9] Joint and muscle pain, especially muscle pain associated with exercise, and weight gain were found to be predictive factors for PPS in our study. However, we were unable to determine from our chart review whether these factors occurred before or in association with the disease. Therefore, it is currently unclear whether or not they are true risk factors or simply consequences of the disease process. Joint and muscle pain can indicate overuse, but may also result from increased weakness. Weight gain may occur before PPS or may result from decreased activity secondary to increased weakness. The exact role of physical activity is currently unclear. Klingman et al[13] found that increased recent physical activity was a predictive factor for PPS; however, two other studies that assessed this factor did not confirm this finding.[10,14] Therefore, the exact role of physical activity still needs further study. In addition,

Klingman et al[13] noted that patients with PPS were more likely to be less disabled at presentation to clinic (and thus were probably more active); however, our study found that PPS patients were significantly more disabled ($p < 0.001$) at presentation to clinic than stable APP controls.

The normal aging process, which is associated with a gradual loss of motor neurons, and a reduction in growth hormone and insulin-like growth factor-1 (IGF-1) may be contributing factors.[11,19-26] Growth hormone and IGF-1 have trophic effects on muscle fibers and peripheral nerves.[27-32] One study[14] found that a greater age at presentation to clinic was a risk factor for PPS, but another study[9] did not confirm this finding.

Based on the results of these studies, it appears that the degree of paralysis at the time of APP (and age at the time of this illness) are risk factors for PPS. The degree of recovery after the acute illness may be important. Time after APP and age may also be risk factors. The exact role of physical activity is unclear because of some contradictory findings; however, it is likely that physical activity that avoids muscle pain is safe. Weight gain, exercising to the point of muscle pain, and activities that cause joint pain should be avoided, since these factors have been found to be associated with PPS and may also prove to be risk factors.

Prognosis of Post-poliomyelitis Syndrome

PPS is considered to be a slowly progressive neuromuscular disease. Even though PPS is rarely fatal, it can produce significant problems in work productivity and general level of functioning. PPS most commonly produces difficulty with mobility and in instrumental activities of daily living, and less commonly in basic activities of daily living.[33] PPS is potentially dangerous in individuals with respiratory muscle weakness as a result of APP and/or PPS, because any further increase in this weakness could result in respiratory failure. In the same way, severe dysphagia could also be life threatening. The effect of PPS on life span has not been studied.

PPS consists of new weakness, fatigue, and pain many years after recovery from APP. Several prospective studies have assessed muscular strength over time in post-polio patients, and a majority have found a slow decline in strength.[34-39] Two studies[40,41] found no decline in strength over time. Isokinetic muscular fatigue was studied in 12 unstable (subjectively weaker) and 8 stable post-polio subjects on two occasions 4 to 5 years apart,[37] and an increase in fatiguability was found only in the stable group. However, the symptoms of general fatigue and pain in PPS have not been studied prospectively. Clinical experience suggests that, in general, these symptoms may slowly increase with time, but that improvement is possible if the patients learn how to manage their new difficulties.

REFERENCES

1. Adams RD, Victor M. *Principles of Neurology.* New York: McGraw-Hill Book Company 1993;641-644.
2. Canadian Pharmaceutical Association. *Compendium of Pharmaceuticals*. Toronto:CK Productions, 1994;1038-1039.
3. Wright PF, Kim-Farley RJ, De Quadros CA, Robertson SE, Scott RM, Ward NA, Henderson RH. Strategies for the global eradication of poliomyelitis by the year 2000. *N Engl J Med* 1991;325:1774-1779.
4. CDC. Progress toward global poliomyelitis eradication, 1985-1994. *JAMA* 1995;273: 1408-1409.
5. Parsons PE. [Letter.] *N Engl J Med* 1991;325:1108.
6. Codd MB, Mulder DW, Kurland LT, Beard CM, O'Fallon WM. Poliomyelitis in Rochester, Minnesota, 1935-1955: epidemiology and long-term sequelae: a preliminary report. In: Halstead LS, Wiechers DO, eds. *Late Effects of Poliomyelitis*. Miami, FL: Symposia Foundation, 1985:121-134.
7. Speier JL, Owen RR, Knapp M, Canine JK. Occurrence of post-polio sequelae in an epidemic population. In: Halstead LS, Wiechers DO, eds. *Research and Clinical Aspects of the Late Effects of Poliomyelitis*. White Plains, NY: March of Dimes Birth Defects Foundation, 1987;39-48.
8. Windebank AJ, Daube JR, Litchy WJ, Codd M, Chao EYS, Kurland LT, Iverson R. Late sequelae of paralytic poliomyelitis in Olmsted County, Minnesota. In: Halstead LS, Wiechers DO, eds. *Research and Clinical Aspects of the Late Effects of Poliomyelitis*. White Plains, NY: March of Dimes Birth Defects Foundation 1987;27-38.
9. Windebank AJ, Litchy WJ, Daube JR, Kurland LT, Codd MB, Iverson R. Late effects of paralytic poliomyelitis in Olmsted County, Minnesota. *Neurology* 1991;41:501-507.
10. Ramlow J, Alexander M, LaPorte R, Kaufmann C, Kuller L. Epidemiology of the post-polio syndrome. *Am J Epidemiol* 1992;136:769-786.
11. Jubelt B, Cashman NR. Neurological manifestations of the post-polio syndrome. *CRC Critl Rev Neurobiol* 1987;3:199-220.
12. Halstead LS, Rossi CD. Post-polio syndrome: clinical experience with 132 consecutive outpatients. In: Halstead LS, Wiechers DO, eds. *Research and Clinical Aspects of the Late Effects of Poliomyelitis*. White Plains, NY: March of Dimes Birth Defects Foundation, 1987;13-26.
13. Klingman J, Chui H, Corgiat M, Perry J. Functional recovery. A major risk factor for the development of postpoliomyelitis muscular atrophy. *Arch Neurol* 1988;45:645-647.
14. Trojan DA, Cashman NR, Shapiro S, Tansey CM, Esdaile JM. Predictive factors for post-poliomyelitis syndrome. *Arch Phys Med Rehabil* 1994;75:770-777.
15. Wiechers DO, Hubbell SL. Late changes in the motor unit after acute poliomyelitis. *Muscle & Nerve* 1981;4:524-528.
16. Wiechers DO. New concepts of the reinnervated motor unit revealed by vaccine-associated poliomyelitis. *Muscle Nerve* 1988;11:356-364.
17. Bennett RL, Knowlton GC. Overwork weakness in partially denervated skeletal muscle. *Clin Orthopedics* 1958;12:22-29.
18. Perry J, Barnes G, Gronley MA. The postpolio syndrome. *Clin Orthopedics Rel Res* 1988;233:145-162.

19. Shetty KR, Mattson DE, Rudman IW, Rudman D. Hyposomatomedinemia in men with post-poliomyelitis syndrome. *J Am Geriatr Soc* 1991;39:185-191.

20. McComas AJ, Upton ARM, Sica REP. Motoneurone disease and ageing. *Lancet* 1973;ii:1477-1480.

21. Stalberg E, Thiele B. Motor unit fibre density in the extensor digitorum communis muscle. *J Neurol Neurosurg Psych* 1975;38:874-880.

22. Tomlinson BE, Irving D. The number of limb motor neurons in the human lumbosacral cord throughout life. *J Neurol Sci* 1977;34:213-219.

23. Rudman D, Kutner MH, Rogers M, Fubin MF, Fleming A, Bain RP. Impaired growth hormone secretion in the adult population. *J Clin Invest* 1981;67:1361-1369.

24. Florini JR, Prinz PN, Vitiello MV, Hintz RL. Somatomedin-C levels in healthy young and old men: relationship to peak and 24-hour integrated levels of growth hormone. *J Gerontol* 1985;40:2-7.

25. Vermeulen A. Nyctohemeral growth hormone profiles in young and aged men: correlation with somatomedin-C levels. *J Clin Endocrinol Metab* 1987;64:884-888.

26. Rao U, Shetty KR, Mattson DE, Rudman IW, Rudman D. Prevalence of low plasma IGF-I in poliomyelitis survivors. *J Am Geriatr Soc* 1993;41:697-702.

27. Froesch ER, Schmid C, Schwander J, Zapf J. Action of insulin-like growth factors. *Ann Rev Physiol* 1985;47:443-467.

28. Hill DJ, Grace CJ, Strain AJ, Milner RDG. Regulation of amino acid uptake and deoxyribonucleic acid synthesis in isolated human fetal fibroblasts and myoblasts: effect of human placental lactogen, somatomedin-C, multiplication-stimulating activity, and insulin. *J Clin Endocrinol Metab* 1986;62:753-759.

29. Roeder RA, Hossner KL, Sasser RG, Gunn JM. Regulation of protein turnover by recombinant human insulin-like growth factor-I in L6 myotube cultures. *Horm Metab Res* 1988;20:698-700.

30. Kanje M, Skottner A, Lundborg G. Effects of growth hormone treatment on the regeneration of rat sciatic nerve. *Brain Res* 1988;475:254-258.

31. Kanje M, Skottner A, Sjoberg J, Lundborg G. Insulin-like growth factor I (IGF-I) stimulates regeneration of sciatic nerve. *Brain Res* 1989;486:396-398.

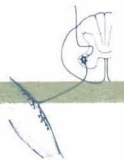
32. Caroni P, Grandes P. Nerve sprouting in innervated adult skeletal muscle induced by exposure to elevated levels of insulin-like growth factors. *J Cell Biol* 1990;110:1307-1317.

33. Grimby G, Thoren Jonsson AL. Disability in poliomyelitis sequelae. *Phys Ther* 1994;74:415-424.

34. Dalakas MC, Elder G, Hallett M, Ravits J, Baker M, Papadopoulos N, Albrecht P, Sever J. A long-term follow-up study of patients with post-poliomyelitis neuromuscular symptoms. *N Engl J Med* 1986;314:959-963.

35. Brown S, Patten BM. Post-polio syndrome and amyotrophic lateral sclerosis: a relationship more apparent than real. In: Halstead LS, Wiechers DO, eds. *Research and Clinical Aspects of the Late Effects of Poliomyelitis*. White Plains, NY: March of Dimes Birth Defects Foundation, 1987:83-98.

36. Finkelman R, Munsat T, Andres P, Thornell B, Brussock C. Alterations of strength in post-polio syndrome. In: Munsat TL, ed, *Post-polio Syndrome*. Boston: Butterworth-Heinemann, 1991;91-103.



37. Grimby G, Hedberg M, Henning GB. Changes in muscle morphology, strength and enzymes in a 4-5-year follow-up of subjects with poliomyelitis sequelae. *Scand J Rehab Med* 1994;26:121-130.

38. Sonies BC, Dalakas MC. Dysphagia in patients with the post-polio syndrome. *N Engl J Med* 1991;324:1162-1167.

39. Agre JC, Grimby G, Rodriquez AA, Einarsson G, Swiggum ER, Franke TM. A comparison of symptoms between Swedish and American post-polio individuals and assessment of lower limb strength—a four-year cohort study. *Scand J Rehab Med* 1995;27:183-192.

40. Munin MC, Jaweed MM, Staas Jr WE, Satinsky AR, Gutlerez G, Herbison GJ. Postpoliomyelitis muscle weakness: a prospective study of quadriceps strength. *Arch Phys Med Rehab* 1991;72:729-733.

41. Windebank AJ, Litchy WJ, Daube JR, Iverson RA. Lack of progression of neurologic deficit in survivors of paralytic polio: a 5-year prospective population-based study. *Neurology* 1996;46:80-84.

Chapter 3

PATHOPHYSIOLOGY OF POST-POLIOMYELITIS SYNDROME

Introduction

As noted in previous chapters, post-poliomyelitis syndrome (PPS) can be defined as a symptom complex of new weakness, fatigue, and pain developing decades after the original acute paralytic poliomyelitis (APP). Although the definitive etiology of PPS has not been universally accepted, a research consensus may be emerging with respect to the cause of the symptoms.

Electrophysiologic Correlates of Post-polio Weakness

The most widely accepted model of new weakness in PPS—that of "peripheral disintegration" of motor units—was originally proposed by Wiechers and Hubbell.[1] To elucidate their hypothesis, background information follows.

Immediately following APP, brain stem and spinal cord motor neurons that persist are capable of elaborating new branches called axonal sprouts (Figure 1). Sprouts may originate

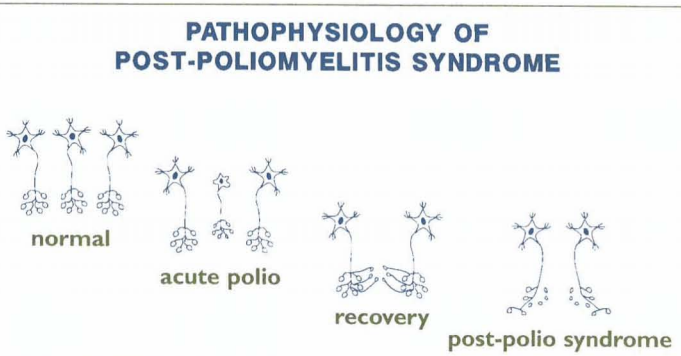
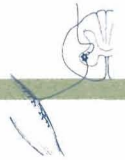


Figure 1. **Normal:** Three normal motor units are presented. **Acute Polio:** Invasion of one motor neuron by poliovirus produces degeneration of the affected motor neuron and denervation of associated muscle fibers. **Recovery:** Recovery after paralytic polio occurs through axonal sprouting from surviving motor neurons with reinnervation of muscle fibers. Muscle fiber hypertrophy may also occur (not illustrated). **Post-polio Syndrome:** Distal degeneration of enlarged motor units with denervation of muscle fibers is believed to be the most likely cause of PPS.



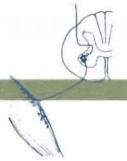
from the terminal axon, from a more proximal unmyelinated axon, or from nodes of Ranvier even more proximal to the motor point. Motor axonal sprouts are capable of reinnervating muscle fibers that have lost their motor innervation due to APP.

Motor axonal sprouting is associated with at least two changes in the structure of motor units (defined as motor neurons and the muscle fibers they innervate). First, axonal sprouting increases the size of the motor unit. In mammals, somatic motor neurons may innervate a variable number of muscle fibers, depending on the muscle studied. Thus, human hand muscles (requiring considerable fine control) are innervated by motor neurons that supply dozens to hundreds of muscle fibers, whereas large muscles such as the quadriceps are divided into motor units consisting of thousands of muscle fibers. After APP, motor unit size can increase by 7- to 8-fold. Thus, a motor neuron in the quadriceps "designed" to support 5000 muscle fibers may support 35,000 or 40,000 muscle fibers in its full capacity for reinnervation after poliomyelitis.

A second major change in motor unit structure relates to fiber type grouping. Muscle fibers comprise at least three histochemical types, depending on contraction characteristics. Ordinarily, muscle fibers from a single motor neuron are distributed in a "mosaic" pattern throughout a muscle fascicle. Because of local sprouting after APP, muscle fibers innervated by the same motor neuron may be clustered in groups. Because motor neurons determine histochemical muscle fiber type, this phenomenon gives rise to fiber type grouping on histochemical analysis of muscle biopsies.

Wiechers and Hubbell[1] proposed that the compensatory enlargement of motor units after APP is not indefinitely stable, and that terminal axonal sprouts degenerate over time (Figure 1). They were able to demonstrate that jitter on single-fiber electromyography (SFEMG), an indirect indicator of terminal axonal integrity (explained below), increased with the number of years after APP. Although no other investigator (including Wiechers in a separate study[2] of vaccine-related APP) was able to replicate these data, the theory proposed to explain the original data has received direct and indirect confirmation over the past 15 years.

Perhaps the best evidence for the Wiechers–Hubbell hypothesis is provided by muscle biopsy studies of patients with PPS. When a muscle fiber loses its innervation, it undergoes progressive atrophy to the point of becoming a tiny "nuclear bag" months after denervation. Muscle fibers that have lost their innervation weeks before a biopsy can display muscle fiber atrophy that is intermediate between a normal muscle fiber and a nuclear bag. Post-polio muscle biopsies contain isolated atrophic angulated fibers,[3] which were presumably denervated shortly



before biopsy, in addition to displaying large numbers of atrophic nuclear bags, some of which may have persisted since the original illness. Isolated atrophic fibers suggest degeneration of isolated terminal axons, as would be predicted by the Wiechers–Hubbell model. In contrast, if PPS were a motor neuron disease (eg, an indolent type of amyotrophic lateral sclerosis), the muscle fibers of entire motor units would be expected to be denervated simultaneously. As the post-polio motor unit often displays fiber type grouping, this phenomenon should be readily detectable because whole sections of muscle fascicle should be undergoing atrophy at the same time. Despite the presence of small groups of atrophic fibers on post-polio muscle biopsies, the predominant conventional histochemical finding is isolated fiber atrophy. Thus, new weakness of PPS is not due to death of motor neurons, but to degeneration of terminal axons.

It must be noted that several predictions arising from this model have not yet been confirmed. For example, there seems to be no more denervation in patients complaining of new post-polio weakness than in subjects with a prior history of APP without new weakness.[3] Moreover, a specialized technique called macro-EMG does not reproducibly appear to detect decreasing motor unit size in patients with PPS, as would be expected if terminal axons are being "pruned" from motor units. Indeed, one careful study appears to demonstrate an increase in motor unit size with time after APP.[4]

Neuromuscular Junction Transmission Defects in Post-polio Fatiguability

"Fatigue" has many implications for a PPS subject. Many patients describe a flu-like generalized fatigue that is associated with defects in concentration and memory. Many others report a decline in strength on continued exertion, which might best be designated "fatiguability" or lack of endurance. Strength usually returns after a short period of rest. In the lay literature, this phenomenon has been designated as the "polio wall." When subjects with PPS have been compared with other medically ill patients, muscle fatiguability (but not generalized fatigue) is reported significantly more often in the PPS patients.[5] Muscle fatiguability in PPS is reminiscent of that occurring in myasthenia gravis, a well-described syndrome of episodic weakness due to defects in neuromuscular junction (NMJ) transmission.

Central and peripheral fatigue in PPS have been attributed to a number of possible causes.[6] Possible causes for central fatigue include chronic pain, respiratory compromise, depression, "type A" behavior, sleep disorders, and dysfunction of the reticular activating system.[7-10] Proposed causes for peripheral fatigue that involve the motor unit include metabolic exhaustion of massively enlarged motor units, NMJ transmission defects, overuse myopathy, and fiber type disproportion.[11-16]

If terminal axonal degeneration is responsible for new weakness in PPS, one could assume that terminal axons cannot be normal one day and gone the next day. It is likely that there is a period of terminal axonal *dysfunction* that may predate degeneration by months to years. The dysfunction of terminal axons provides therapeutic options that would not be tenable in the case of irreversible loss of terminals.

How might terminal axonal dysfunction manifest itself? The major clinically relevant function of a terminal motor axon is the release of acetylcholine upon depolarization. Acetylcholine rapidly diffuses across the junction between the axon and the muscle end plate,

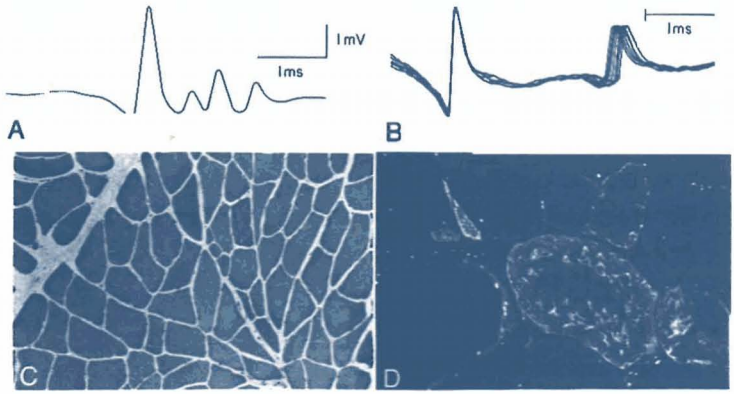
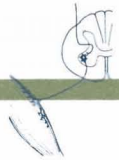


Figure 2. Single-fiber electromyographic studies (**A** and **B**) and muscle biopsy histopathologic studies (**C** and **D**) of the right deltoid muscle of an asymptomatic patient. The patient was a 64-year-old man who had had paralytic poliomyelitis involving all four limbs at the age of 9 and whose 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, 74 μs; 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). Reprinted by permission of the *New England Journal of Medicine*, Cashman NR, Maselli R, Wollman RL, Ross R, Simon R, Antel JP. Late denervation in patients with antecedent paralytic poliomyelitis. Volume 317, pages 7-12. Copyright 1987, Massachusetts Medical Society.



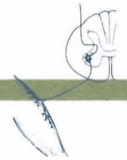
triggering muscle fiber depolarization mediated by the postsynaptic acetylcholine receptors. Acetylcholine is rapidly degraded in the NMJ and end plate by acetylcholinesterase, limiting its duration of action.

Many authors have reported NMJ transmission defects in individuals following APP. Findings include increased jitter on SFEMG, decrement on repetitive stimulation, and increased sensitivity to non-depolarizing muscle relaxants. Moreover, muscle immunohistochemical studies for neural cell adhesion molecule (N-CAM) also suggest a profound NMJ instability (Figure 2).[3]

SFEMG is a specialized electromyographic technique to examine electrical events in muscle occurring in the small receptive volume of the SFEMG needle. One important SFEMG parameter that can be quantified and objectively compared between different groups of patients is *jitter*. In normal muscle, the depolarizations of two muscle fibers innervated by the same motor neuron are essentially time-locked, that is, depolarization of one muscle fiber occurs at a set time in relation to another muscle fiber. This is due to uniform conduction of a motor axonal impulse down all branches of a motor axon. However, if one terminal axon (or sprout) has inconsistent conduction velocity or release of suboptimal acetylcholine, depolarization of this muscle fiber can be blocked or slowed to a variable degree. On the oscilloscope screen, this potential appears to "jitter" back and forth with relation to the triggering potential. Although early studies of jitter in PPS were initially interpreted to demonstrate ongoing denervation and reinnervation, they could also be regarded as reflecting defective NMJ transmission. This notion is supported by more recent studies of post-polio NMJ defects using stimulation SFEMG.[17] NMJ transmission was "stressed" using artificially high rates of nerve stimulation. SFEMG jitter was increased in post-polio patients at high rates of stimulation in contrast to normal controls, who rarely displayed this phenomenon.[17] Moreover, NMJ defects can be ameliorated by the anticholinesterase edrophonium, further implicating defective release of acetylcholine in PPS.[16]

Increased single-fiber jitter observed by many workers was not the first suggestion of NMJ transmission defects in PPS. Hodes[18] demonstrated a decrement of the compound motor action potential on repetitive stimulation studies of subjects with prior APP. More recent studies demonstrate that a decrement is more readily apparent at high rates of stimulation, suggesting that acetylcholine release may be a limiting factor in NMJ transmission.[19]

Post-polio patients also demonstrate increased sensitivity to non-depolarizing muscle relaxants, including D-tubocurarine, pancuronium, and gallamine.[20] This study, validating an impression of practicing anesthesiologists, also suggests that acetylcholine release may be suboptimal in motor units affected by APP.



Morphologic Evidence of Neuromuscular Junction Defects

Post-polio neuromuscular junctions have been directly examined by electron microscopy,[21] showing dilated or bizarre terminal axons with reduced vesicle size. In addition, post-polio muscle has been studied histochemically with N-CAM antibodies.[3] Muscle N-CAM, confined in normal muscle to satellite cells, end plates, intramuscular nerves, and some other regions, becomes diffusely expressed in muscle fibers following denervation.[22] In experimental animals, increased N-CAM immunoreactivity can be demonstrated within 2 days of nerve transection, long preceding conventional criteria of denervation.[22] Thus, N-CAM immunoreactivity in normal-sized myofibers may suggest that the fiber has been recently denervated, and may have been destined either to be reinnervated or to undergo progressive atrophy. Paralysis of muscle by treating its supplying nerve with tetrodotoxin also induces widespread N-CAM immunoreactivity,[21] suggesting that defective NMJ transmission could also prompt its accumulation. However, our own unpublished studies demonstrate that N-CAM immunoreactivity is not observed in muscles of patients with myasthenia gravis, suggesting that intermittent or mild transmission defects do not trigger myofiber N-CAM expression. In PPS and in individuals with APP, N-CAM expression in non-atrophic myofibers can reach 10% or more.[3] The fact that permanently denervated fibers (angular atrophic myofibers) are only detected at 1% or less of a muscle biopsy[3] strongly suggests that post-polio muscle fibers are continually poised at a critical threshold for adequate transmission of nerve impulses. Widespread N-CAM immunoreactivity is consistent with electrophysiologic data showing profound and widespread NMJ transmission defects.

Conclusions

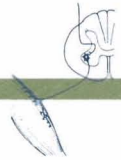
As our understanding of PPS evolves, it may be fruitful to consider the symptoms of PPS to be due to two types of lesions of the motor unit: a progressive lesion and a fluctuating lesion. The progressive lesion is degeneration of terminal axons, resulting in slowly progressive new weakness that is irreversible. The appearance of isolated angular fibers appears to be the best morphologic correlate of this process.

A "fluctuating lesion" in PPS might give rise to the symptoms of muscle fatiguability and generalized fatigue. These symptoms may change over the course of minutes to days, and are more consistent with a dysfunction of terminal axons. It is possible that defective synthesis and release of acetylcholine into the NMJ participates in the NMJ transmission defects underlying these symptoms. The evidence for existence of this lesion is provided by muscle biopsy studies and innumerable electrodiagnostic studies showing defective NMJ transmission; studies demon-

strating defective function of NMJ transmission under artificially induced stress of high rates of repetitive stimulation; and sensitivity of post-polio muscle to non-depolarizing muscle relaxants. Thus, agents that support NMJ transmission may provide novel therapies for PPS.

REFERENCES

1. Wiechers DO, Hubbell SL. Late changes in the motor unit after acute poliomyelitis. *Muscle Nerve* 1981;4:524-528.
2. Wiechers DO. New concepts of the reinnervated motor unit revealed by vaccine-associated poliomyelitis. *Motor Nerve* 1988;11:356-364.
3. Cashman NR, Maselli R, Wollman RL, Ross R, Simon R, Antel JP. Late denervation in patients with antecedent paralytic poliomyelitis. *N Engl J Med* 1987;317:7-12.
4. Stalberg E, Grimby G. Dynamic electromyography and muscle biopsy changes in a 4-year follow-up study of patients with a history of polio. *Muscle Nerve* 1995;18:699-707.
5. Berlly MH, Strauser WW, Hall KM. Fatigue in post-polio syndrome. *Arch Phys Med Rehabil* 1991;72:115-118.
6. Gow PJ, Stokes M, Edwards RHT. Investigations of neuromuscular performance in post-polio patients: a practical approach. In: Halstead LS, Wiechers DO, eds. *Research and Clinical Aspects of the Late Effects of Poliomyelitis*. White Plains, NY: March of Dimes Birth Defects Foundation, 1987:293-300.
7. Bruno RL, Frick NM. Stress and "type A" behavior as precipitants of post-polio sequelae: the Felician/Columbia Survey. In: Halstead LS, Wiechers DO, eds. *Research and Clinical Aspects of the Late Effects of Poliomyelitis*. White Plains, NY: March of Dimes Birth Defects Foundation, 1987:145-155.
8. Fischer DA. Sleep-disordered breathing as a late effect of poliomyelitis. In: Halstead LS, Wiechers DO, eds. *Research and Clinical Aspects of the Late Effects of Poliomyelitis*. White Plains, NY: March of Dimes Birth Defects Foundation, 1987:115-120.
9. Kohl SJ. Emotional responses to the late effects of poliomyelitis. In: Halstead LS, Wiechers DO, eds. *Research and Clinical Aspects of the Late Effects of Poliomyelitis*. White Plains, NY: March of Dimes Birth Defects Foundation, 1987:135-143.
10. Halstead LS. Post-polio syndrome: definition of an elusive concept. In: Munsat TL, ed. *Post-polio Syndrome*, Boston, MA: Butterworth-Heinemann, 1991:23-28.
11. McComas AJ, Upton ARM, Sica REP. Motoneurone disease and ageing. *Lancet* 1973;2:1477-1480.
12. Jubelt B, Cashman NR. Neurological manifestations of the post-polio syndrome. *CRC Critical Reviews in Neurobiol* 1987;3:199-220.
13. Grimby G, Einarsson G. Muscle morphology with special reference to muscle strength in post-polio subjects. In: Halstead LS, Wiechers DO, eds. *Research and Clinical Aspects of the Late Effects of Poliomyelitis*. White Plains, NY: March of Dimes Birth Defects Foundation, 1987:265-274.
14. Munsat TL, Andres P, Thibodeau L. Preliminary observations on long-term muscle force changes in the post-polio syndrome. In: Halstead LS, Wiechers DO, eds. *Research and Clinical Aspects of the Late Effects of Poliomyelitis*. White Plains, NY: March of Dimes Birth Defects Foundation, 1987:329-334.



15. Perry J, Barnes G, Gronley JK. The postpolio syndrome; an overuse phenomenon. *Clin Orthopedics Rel Res* 1988:233:145-162.

16. Trojan DA, Gendron D, Cashman NR. Anticholinesterase-responsive neuromuscular junction transmission defects in post-poliomyelitis fatigue. *J Neurol Sci* 1993;114:170-177.

17. Trojan DA, Gendron D, Cashman NR. Stimulation frequency-dependent neuromuscular junction transmission defects in patients with prior paralytic poliomyelitis. *J Neurol Sci* 1993;118:150-157.

18. Hodes R. Electromyographic study of defects of neuromuscular transmission in human poliomyelitis. *Arch Neurol Psych* 1948;60:457-473.

19. Trojan DA, Gendron D, Cashman NR. Repetitive stimulation studies in post-poliomyelitis syndrome [Abstract in press]. *Arch Phys Med Rehabil* 1996.

20. Gyermek L. Increased potency of nondepolarizing relaxants after poliomyelitis. *J Clin Pharm* 1990;30:170-173.

21. Maselli RA, Wollmann R, Roos R. Function and ultrastructure of the neuromuscular junction in post-polio syndrome. *Ann NY Acad Sci* 1995;753:129-137.

22. Covault J, Sanes JR. Neural cell adhesion molecule (N-CAM) accumulates in denervated and paralyzed skeletal muscle. *Proc Nat Acad Sci USA* 1985;82:4544-4548.

Chapter 4

Differential Diagnosis of Post-poliomyelitis Syndrome

Introduction

The differential diagnosis of post-poliomyelitis syndrome (PPS) must depend on the *diagnosis* of PPS, for which there is no complete consensus at present. PPS is known by at least a dozen overlapping terms, including "late effects of polio," "post-polio sequelae," and "post-polio muscular atrophy." The designation "syndrome" (from the Greek *syn*, together, and *drome*, running) is applicable to PPS because the three major symptoms, new weakness, fatigue, and pain, often occur together. The term "late sequelae of poliomyelitis" lacks the implication of an underlying common etiology suggested by "syndrome." The term "post-polio muscular atrophy" (PPMA) may refer to only a subgroup of those suffering from PPS. Indeed, PPMA may be a late manifestation of the PPS disease process.[1] Thus, in the absence of a universally accepted etiology or a definitive diagnostic test, PPS may be the most precise term for these symptoms that does not exclude important features of the syndrome.

Differential Diagnosis

The diagnosis of PPS is clinically based. There are many medical and musculoskeletal conditions that must be considered in a patient with previous acute paralytic polio (APP) presenting with new difficulties. Many patients with childhood APP have developed distrust of the medical profession, and will frequently attend a post-polio clinic without having seen a physician for decades. In this situation, the first responsibility of a PPS specialist is to be cognizant of illnesses that may result in symptoms reminiscent of PPS, but which have little or nothing to do with APP. For example, pain, weakness, and fatigue can be a manifestation of hypothyroidism or rheumatoid arthritis. Medical diseases (eg, cardiac, hematologic, endocrine, cancer, chronic systemic infections) must also be considered.

Other syndromes may be precipitated or accelerated by APP, but may not constitute a true PPS. Chronically abnormal gait or weight-bearing may give rise to tendinitis and bursitis. Other "musculoskeletal" syndromes to consider are osteoarthritis, biomechanical deficits in gait (such as genu recurvatum), repetitive injury syndromes (such as carpal tunnel syndrome), and failure of previous orthopedic surgical procedures (such as a failed arthrodesis).

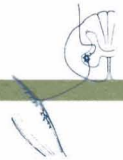


TABLE 1

NEUROLOGIC DISEASES TO EXCLUDE IN DIAGNOSING PPS*

- Adult spinal muscular atrophy
- Amyotrophic lateral sclerosis
- Cauda equina syndrome
- Cervical spondylosis
- Chronic inflammatory demyelinating polyneuropathy
- Diabetic amyotrophy
- Entrapment neuropathy
- Heavy metal toxicity
- Inflammatory myopathy
- Multifocal motor conduction block
- Multiple sclerosis
- Myasthenia gravis
- Parkinson's disease
- Peripheral neuropathy
- Radiculopathy
- Spinal cord tumor
- Spinal stenosis

*These diseases may also occur concurrently with PPS.

The post-polio patient is not immune to development of other neurologic diseases (Table 1). In the author's experience with over 1000 post-polio patients, new multiple sclerosis has been diagnosed four times, Parkinson's disease twice, and spinal cord tumor, inflammatory myopathy, and myasthenia gravis once each.

Other neurologic syndromes that might be mistaken for PPS include diseases of the lower motor neurons or peripheral nerves, such as adult spinal muscular atrophy, chronic inflammatory demyelinating polyneuropathy, diabetic amyotrophy, and heavy metal toxicity. Other mechanical disorders include lumbar spinal stenosis, multiple disc herniation with root entrapment, entrapment neuropathies, and cauda equina syndrome. Amyotrophic lateral sclerosis must also be considered, although the frequency of this disease is not increased in the post-polio patient population.

Fatigue syndromes could conceivably be confused with PPS. Although many features of myasthenia gravis, including fatigue and muscle fatiguability, occur in PPS, this has resulted in diagnostic confusion only once in the authors' experience. Sleep apnea may sometimes present as fatigue and perceived subjective weakness, and has been the primary cause of new symptoms in several patients in our post-polio clinic.

Fibromyalgia in a Post-polio Clinic

We have found that fibromyalgia syndrome (FS) occurs frequently in a post-polio clinic, and can mimic some of the symptoms of PPS, primarily pain and fatigue.[2] FS is a common musculoskeletal disorder, characterized by generalized pain and tenderness. Fatigue and non-restorative sleep also occur commonly.[3] The American College of Rheumatology criteria for FS[4] include at least a 3-month history of widespread pain and the finding of 11 or more of 18 specific tender points on physical examination.

We studied the frequency and clinical characteristics of FS in 105 patients serially presenting to the Montreal Neurological Hospital post-polio clinic during an 18-month period. Ten patients did not have past APP and were excluded. Ten (10.5%) met the criteria for FS, and another 10 (10.5%) met the criteria for "borderline FS," which we defined as a history of widespread pain of at least 3 months' duration, and the finding of 5 to 10 tender points from a possible 18 on physical examination. Six of 10 FS patients and 5 of 10 "borderline FS" patients also met the criteria for PPS (new muscle weakness and fatigue in patients with at least 10 years of functional stability following recovery from APP, and no other medical or neurologic conditions that could explain their symptoms). The clinical characteristics of FS patients with past APP were similar to those of FS patients in other patient populations (ie, a female predominance of 80% and a similar mean age at presentation of 50.8 years). We compared the clinical characteristics of FS patients who had recovered from APP with those of patients with past APP without FS. Patients with FS were significantly different from APP patients without FS in terms

of female sex (80% vs 40%; $p = 0.04$), and the complaint of muscle pain (90% in FS vs 40% in the non-FS group; $p = 0.04$). There was a trend toward greater frequency of general fatigue in patients with FS (100% vs 71%; $p = 0.06$).

Our post-polio patients with FS were treated with previously described treatments for FS. Six of nine patients with FS for whom outcome is known reported improvement in symptoms with low-dosage amitriptyline 10 to 50 mg every evening. Some patients also reported improvement with other treatments such as cyclobenzaprine, fluoxetine, naproxen, aerobic exercise, and use of a cervical pillow. Of interest is that Gawne and Halstead[5] have reported success in treating fatigue in PPS with low-dose nighttime tricyclic antidepressants; however, the FS status of these patients was not stated. Therefore, the usual treatments for FS may have a wider applicability in post-polio patients.

Based on our study, we found that FS occurs frequently in a post-polio clinic, and that the clinical characteristics of FS in patients with past APP are similar to those of other FS patient populations. Some symptoms of FS (especially pain and fatigue) can mimic PPS. FS and PPS can also occur concurrently, and a recent finding of low circulating levels of insulin-like growth factor-1 (IGF-1) both in FS[6] and in previous APP[7,8] suggests a hypothesis for the common concurrence of these two syndromes. FS in PPS patients can respond to specific treatment for FS. For this reason, it is important to diagnose and treat FS in a post-polio patient with new symptoms.

REFERENCES

1. Cashman NR, Maselli R, Wollmann R, Simon R, Heidkamp P, Anetl JP. New muscle atrophy as a late symptom of the post-poliomyelitis syndrome. *Clin Ecol* 1987;5:11-13.
2. Trojan DA, Cashman NR. Fibromyalgia is common in a postpoliomyelitis clinic. *Arch Neurol* 1995;52:620-624.
3. Wolfe F. Fibromyalgia: the clinical syndrome. *Rheum Dis Clin North Am* 1989;15:1-18.
4. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. *Arthritis Rheum* 1990;33:160-172.
5. Gawne AC, Halstead LS. Post-polio syndrome: pathophysiology and clinical management. *Crit Rev Phys Rehab Med* 1995;7:147-188.
6. Bennett RM, Clark SR, Campbell SM, Burckhardt CS. Low levels of somatomedin C in patients with the fibromyalgia syndrome. *Arthritis Rheum* 1992;35:1113-1116.
7. Shetty KR, Mattson DE, Rudman IW, Rudman D. Hyposomatomedinemia in men with postpoliomyelitis syndrome. *J Am Geriatr Soc* 1991;185:185-191.
8. Rao U, Shetty KR, Mattson DE, Rudman IW, Rudman D. Prevalence of low plasma IGF-1 in poliomyelitis survivors. *J Am Geriatr Soc* 1993;41:697-702.

Chapter 5

Current Management of Post-poliomyelitis Syndrome

Introduction

Although there is currently no specific treatment for post-poliomyelitis syndrome (PPS), patients with this condition can improve with appropriate management.[1] Many patients may benefit from at least some of the measures described below. Because of the great variety of symptoms reported by PPS patients, an interdisciplinary approach to management is probably most effective. The team can include a primary care physician, physiatrist, neurologist, pulmonary specialist, psychiatrist, orthopedist, and rheumatologist. Other health personnel who can be involved in the care of these patients are physical therapists, occupational therapists, respiratory therapists, psychologists, social workers, dieticians, and orthotists.

Because there is currently no diagnostic test for PPS, this syndrome is diagnosed by excluding other medical and neurologic disorders that can produce similar symptoms. In addition, the symptom of fatigue is extremely common in the general population, and may be caused by a variety of disorders. There are also many potential causes for pain and weakness. It is important that these other causes be identified and treated before new symptoms in a post-polio patient are attributed to PPS. (Differential diagnosis was discussed in detail in the previous chapter.)

In a post-polio patient presenting with complaints of new weakness, fatigue, and/or pain, we recommend that a thorough medical and neurologic examination, with screening blood tests to exclude PPS mimics, be performed first. Laboratory tests may include complete blood count, SMAC (sodium, potassium, chloride, HCO_3, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, total protein, albumin, total bilirubin, magnesium, AST, ALT, LDH, alkaline phosphatase, creatinine kinase), thyroid-stimulating hormone, erythrocyte sedimentation rate, and serum protein electrophoresis. Some investigators[2] recommend that standard electromyography (EMG)/nerve conduction studies be performed for all four extremities on all patients to confirm evidence of previous motor neuron loss and to exclude peripheral nerve dysfunction and other neuropathic and myopathic conditions. In 100 consecutive post-polio patients, Gawne and Halstead[2] found evidence of other neuropathic conditions in 49%. However, as mentioned, we recommend performing EMG studies only in those patients who have an unclear history of

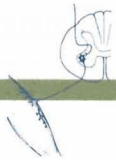
previous acute paralytic poliomyelitis (APP) or who lack the usual findings of previous APP on physical examination. Other studies such as nerve conduction, F-waves, and H-reflexes should be performed when clinically indicated to rule out other neurologic disorders. This is especially true for those patients who present with complaints of numbness and/or sensory deficits on neurologic examination. Plain radiographic studies are frequently needed to evaluate joint dysfunction. In addition, computed tomography scans and/or magnetic resonance imaging (MRI) may also be needed to exclude conditions such as spinal stenosis, radiculopathy, or cervical myelopathy. In general, EMG is less helpful in excluding these conditions in patients with past APP because widespread denervation obscures any recent local denervation. Pulmonary function tests should be performed in virtually all patients because unexpected deficits can be present even in patients without a history of previous or recent respiratory dysfunction. Sleep studies may be necessary in patients with symptoms suggestive of sleep apnea (snoring, frequent waking, daytime fatigue, morning headaches, impaired cognition, irritability, anxiety, cyanosis, and depression). Swallowing studies with videofluoroscopy may also be necessary.

In this review, we will present general guidelines for the managment of the main symptoms of PPS—new weakness, fatigue, and pain. Pulmonary dysfunction and dysphagia will be discussed briefly.

■ Management of Weakness

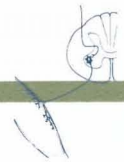
The management of new weakness in a post-polio patient can include a strengthening exercise program, an aerobic exercise program, stretching to decrease or prevent contractures, avoidance of muscular overuse (exercising to the point of muscle pain and fatigue), bracing, and use of assistive devices.

Exercise in post-polio patients has been a controversial topic for many years, primarily because of case reports of overwork weakness in these patients.[3,4] These clinical findings were supported by studies in denervated muscles of rats.[5-8] However, more recently, several studies have found that exercise can result in an increase in strength in post-polio patients many years after the acute illness. Feldman[9] and Feldman and Soskolne[10] were the first to report in more recent years a beneficial effect of an exercise program many years after APP. They treated 32 "PPS" muscles in six post-polio patients with an attenuated, "non-fatiguing," isotonic strengthening exercise program for at least 24 weeks, and found that 14 muscles improved in strength, 17 muscles maintained strength, and one muscle decreased in strength. However, the method of strength assessment and the changes in strength were not reported. Einarsson and



Grimby[11] and Einarsson[12] studied the effects of a 6-week, three-times-per-week, isokinetic and isometric exercise program for the quadriceps muscles (3+ or better on manual muscle testing) in 12 post-polio patients. They found a mean increase of 29% in isometric strength and a mean increase of 24% in isokinetic strength. Muscle biopsy studies did not show a higher occurrence of histopathologic findings after training, although citrate synthase concentration increased non-significantly. Fillyaw and coworkers[13] assessed the effect of a long-term (2-year), every-other-day, non-fatiguing, isotonic exercise program in 17 PPS patients. In each patient, one biceps muscle and one quadriceps muscle were randomly assigned to the exercise program. In 16 of 17 subjects, the maximum amount of weight a subject could lift 10 times increased by a mean of 77.7%. A significant increase of 8.4% in the maximum isometric torque occurred in the exercised muscles over the 2 years, whereas a non-significant change of −4.3% occurred in the non-exercised muscles. The authors concluded that PPS patients can benefit from a non-fatiguing, long-term exercise program, but that quantitative muscle strength testing should be performed at least every 3 months to prevent overwork weakness. Agre and coworkers[14] have also assessed the effect of a 12-week isotonic and isometric home exercise program in seven post-polio patients. The maximum isometric strength (maximum voluntary contraction, MVC) significantly increased by 36%, endurance time at 40% MVC increased by 21%, and the tension time index increased by 18%. Fiber density, jitter, blocking, median macro-EMG amplitude, and creatine kinase did not change significantly with the exercise program.

In addition to strengthening exercise, aerobic exercise is also beneficial in post-polio patients. The effect of an aerobic exercise program on a bicycle ergometer was assessed in 37 post-polio patients by Jones and co-workers.[15] They found that the average level of aerobic fitness in post-polio patients was 5.6 metabolic equivalents, similar to that seen in patients just after a myocardial infarction.[16] Patients were assigned either to a 13- to 30-minute, three-times-per-week, 16-week exercise program, at up to 70% of maximum heart rate, or to no exercise. The exercised patients experienced significant increases in power attained during exercise, duration of exercise, maximum expired volume per unit time, and maximum oxygen consumption (VO_{2max}). The non-exercising controls showed no improvement in these variables. The training effects in the exercising post-polio patients were similar to those observed in age-matched normals previously reported in the literature. Kriz and colleagues[17] studied the effect of a 16-week, upper extremity aerobic exercise program (70% to 75% of heart rate reserve) on a cycle ergometer in 20 post-polio patients. Patients were randomly assigned either to the exercise program or to no exercise. The exercise group experienced a significant improvement com-



pared with the non-exercise group with regard to oxygen consumption, carbon dioxide production, minute ventilation, power, and exercise time. The 19% improvement in cardiovascular fitness was similar to that previously reported in other populations. Dean and Ross[18] also studied the effects of an aerobic exercise program in 20 post-polio patents who were randomly assigned to exercise on a horizontal treadmill or to no exercise. The training occurred three times per week for 6 weeks at 55% to 70% of age-predicted maximum heart rates. Trained subjects showed a significant improvement in economy or energy cost of walking, and thus walking duration, whereas the untrained subjects experienced no changes. No change was observed in cardiorespiratory conditioning.

In summary, exercise has been shown to be beneficial in post-polio patients, even in muscles where new weakness has been reported. The exact exercise prescription is dependent on a number of factors. Isometric exercise is most useful in muscles with less than grade 3 strength (Medical Research Council [MRC] Scale) or in muscles over a painful joint. An isotonic exercise program is most useful in muscles with grade 3 or better strength and without a painful joint. Isokinetic exercise can be used when equipment is available. An aerobic exercise program such as using a bicycle ergometer, walking, or swimming can also be useful, but preferably should be an activity that the patient enjoys in order to increase compliance. A warm-up and cool-down period with stretching exercises should also be included.[2] Some patients may also benefit from more agressive stretching of contractures (if no contraindications exist), such as knee flexion contractures and ankle plantarflexion contractures to improve gait and stability. For the first few weeks, it is best for the patient to be monitored carefully (a few times per week), to ensure that the exercise prescription is being followed correctly and that overuse of muscles and joints does not occur. Once the patient understands the exercise program well, and demonstrates the ability to self-monitor, regular follow-up every few months is reasonable.[19]

Even though several different types of exercise have been shown to be beneficial in the late post-polio patient, exercise should be used judiciously, and should be avoided completely in some patients. Muscle groups that are being overused may benefit from rest or supportive devices such as braces. Studies have not assessed the effect of exercise programs on patient function and general well-being, and the long-term effects of exercise in these patients are still unclear.

Overuse of muscles must be avoided in post-polio patients. In several case reports, muscle overuse in patients with past APP was thought to be the cause of increased weakness.[3] This new

weakness may be permanent. Perry and coworkers[20] performed dynamic electromyography (in quadriceps, soleus, lower gluteus maximus, and long head of biceps femoris) during gait in 34 PPS patients, and found evidence of overuse (compared with normals). This occurred primarily in the biceps femoris (82%) and quadriceps (53%). The usefulness of creatine kinase (CK) levels in the monitoring of overuse in post-polio patients is unclear; however, Waring and McLaurin[21] found a significant correlation between CK levels and distance walked during ambulatory activities in the previous 24 hours, indicating that CK could be a marker of overuse.

In addition, in one case report,[22] CK was found to be markedly elevated in a post-polio patient with symptoms of weakness, fatigue, and pain. With a reduction in exercise, plasma CK levels decreased and symptoms resolved.

In a retrospective study of lower-extremity orthotic management for ambulation in 104 post-polio clinic patients, Waring and coworkers[23] found that 78% of patients noted that appropriate orthotic prescription subjectively improved ability to walk, increased perceived walking safety, and reduced pain. Clark and co-workers[24] have described some of the more common biomechanical deficits, and their orthotic management, in post-polio patients. These include inadequate dorsiflexion in swing, dorsiflexion collapse in stance, genu recurvatum (knee hyperextension), genu valgum (valgus deformity at the knee), and mediolateral ankle instability. In some patients, strengthening exercises may be tried first to control these deformities. If this is impossible, or not useful, orthoses may be used.

Inadequate dorsiflexion occurs secondary to weakness of ankle dorsiflexors and results in a foot drop and a tendency to fall or trip. This problem can be treated with an ankle-foot orthosis (AFO). Dorsiflexion collapse during stance can occur secondary to weak extensor muscles at the hips, knees, and ankles. This can be managed either with canes, crutches, or AFOs. Genu recurvatum in polio patients is most commonly caused by quadriceps weakness, and the resultant tendency of the patient to "lock" the knee to improve stability of the lower extremity. This deformity can cause pain and decreased efficiency of ambulation secondary to the increase in movement at the knee. In patients with mild weakness of the quadriceps, a knee orthosis or even AFO can be used to control the deformity; however, in patients with more severe weakness (MRC 3 or less), a knee-ankle-foot orthosis (KAFO) is necessary. Genu valgum deformity is usually caused by weakness of hip abductors, which causes the patient to lean laterally in stance phase to reduce the demand on this muscle group. This can also cause pain and increased energy expenditure with resultant decreased function. A KAFO with

padded components on the proximal and medial tibia and distal femoral condyles is used to manage this deformity. Mediolateral ankle and subtalar joint instability is produced by weak or absent foot and ankle muscles. This can be treated with foot orthoses or an AFO.[24] In addition to orthoses, other assistive devices that may be useful for post-polio patients to improve mobility and safety are canes, crutches, manual wheelchairs, electric wheelchairs, and motorized scooters.

Management of Fatigue

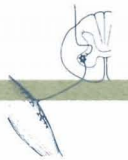
Excessive fatigue in PPS patients may be managed with the use of energy conservation techniques, lifestyle changes, pacing, and taking regular rest periods or naps. Anecdotally, tricyclic antidepressants may be helpful for fatigue, possibly by improving sleep or by other more direct effects on central neurotransmission.[2] The anticholinesterase pyridostigmine may be useful as well (see below and Chapter 6).

Energy conservation techniques may include discontinuing some unnecessary energy-consuming activities (eg, making the bed), using a "handicapped" license plate, sitting instead of standing, moving the location of certain items and supplies to make them more easily accessible (eg, washer and dryer on first floor, not in basement), and using an electric scooter for longer distances. Lifestyle changes may include discontinuing certain activities such as volunteer work, changing to a more sedentary employment, or working part-time. Taking regular naps during the day, especially in the early afternoon, is helpful in the management of general fatigue, and patients (even working patients) should be encouraged to do this.

Agre and Rodriquez[25] found that pacing was helpful to reduce muscle fatigue. Seven symptomatic post-polio patients were studied on three separate occasions at least 1 week apart with three different exercise protocols. Patients were found to have less local muscle fatigue, increased work capacity, and improved recovery of strength after activity when they were allowed to take regular rest periods during an isometric endurance test of the quadriceps at 40% MVC than during a continuous isometric contraction of the quadriceps at 40% MVC. Therefore, regular rest periods during activity should be encouraged.

Management of Pain

Pain in post-polio patients may occur from a number of causes, and management is dependent upon etiology. Pain may be caused by muscle abnormalities, joint and soft tissue abnormalities, and other superimposed neurologic abnormalities. Overuse is the most likely etiology of many



of the pain syndromes. The location of pain appears to be dependent on the method of locomotion.[26] Ambulatory patients reported a high incidence of pain in the lower extremities and lower back, whereas patients who used wheelchairs or crutches reported more pain in the upper extremities.[26]

Common muscular causes for pain include a "post-polio muscular pain,"[2] muscle overuse, muscle cramps, fasciculations, and fibromylagia.[27] "Post-polio muscular pain" may occur in muscles previously affected by APP, and is usually described as an aching sensation similar to that experienced at the time of APP. It typically occurs at the end of the day and is aggravated by activity.[2] Patients can also experience muscle pain with activity. Painful muscle cramps occur either with activity or at the end of the day. Muscle cramps and muscle pain with activity are most likely secondary to overuse. These types of pain should be avoided. Management can include reduction of activity, taking rest periods during activity (pacing), use of moist heat and stretching, use of assistive devices, and lifestyle modifications. Fasciculations are a sign of previous motor neuron damage, and are reported by patients with APP. Fibromyalgia occurs commonly in patients presenting to a post-polio clinic (see Chapter 4), and can be treated with amitriptyline, cyclobenzaprine, aerobic exercise, and other measures.[27]

Joint and soft tissue abnormalities include osteoarthritis, tendinitis, bursitis, ligamentous strain, joint deformities, and failing joint fusions. Because of weakness from APP, post-polio individuals may use certain joints and extremities in abnormal ways, which may predispose them to injury of joints, tendons, bursae, and ligaments. In a cross-sectional study of 61 post-polio patients, the prevalence of radiographically determined moderate to severe osteoarthritis of the hand and wrist was 13%, but the prevalence of mild osteoarthritis in the same joints was 68%. Associated factors for mild osteoarthritis were age greater than 50 years, lower extremity weakness, high current locomotor disability, and high current use of assistive devices.[28] In addition, abnormal forces around joints may produce joint deformities such as genu recurvatum and genu valgum (discussed above). Many of these causes of pain are treatable, at least to some degree. Treatments may include modification of extremity use, physiotherapy for use of physical modalities (eg, ice, superficial heat, ultrasound, transcutaneous electrical nerve stimulation [TENS]), strengthening, orthoses to control joint deformities and failing joint fusions, assistive devices, non-steroidal anti-inflammatory medications, acetaminophen, and rarely, steroid injections or surgery. Stretching of tight tendons and soft tissues may be helpful but in certain situations should be avoided, because some contractures may be biomechanically beneficial for the patient.[29,30]

Superimposed neurologic disorders that can cause pain include peripheral neuropathies, radiculopathies, and spinal stenosis. Electromyographic findings in 100 consecutive post-polio patients revealed a high prevalence of carpal tunnel syndrome (35%). Other neuropathies that were found included ulnar neuropathy at the wrist (2%), peripheral neuropathy (3%), carpal tunnel syndrome and ulnar neuropathy (3%), brachial plexopathy (1%), radiculopathy (4%), and tibial neuropathy (1%).[31] Werner and coworkers[32] found that use of assistive devices is a major risk factor for carpal tunnel syndrome in post-polio patients. Treatments for carpal tunnel syndrome can include splinting,[33] use of pads on canes or crutches, or use of a special grip for canes and crutches that places the wrist in a more neutral position and increases the weight-bearing surface of the hand.[2] For patients with lumbosacral radiculopathies or low back pain, use of lumbosacral corsets, shoe lifts, back supports, or pelvic supports may be helpful. Spinal stenosis may be treated with exercise, use of a cane, TENS, and a lumbosacral orthosis. In some cases (for peripheral neuropathies, radiculopathies, and spinal stenosis) surgery may be necessary.

Pulmonary Dysfunction

Symptoms of respiratory dysfunction are common in patients with past APP[34]; however, compromised lung function may occur in post-polio individuals whether or not shortness of breath is present.[35] Respiratory compromise occurs primarily in those individuals who required ventilation at the time of acute polio, but may also occur in those who do not report previous respiratory involvement. Risk factors for respiratory compromise more than 35 years after APP are the need for ventilation at APP and age at APP of more than 10 years.[35] Manifest hypoventilation is rare in post-polio patients, and was reported to be present in only 2 of 40 patients who had respiratory and non-respiratory APP at least 30 years previously.[36] However, as many as 87.5% of those who were initially weaned from a ventilator may again require the use of a ventilator.[37]

Post-polio patients with late-onset respiratory insufficiency lose vital capacity at rates of 60% to 90% greater than that observed in normals.[38,39] Respiratory muscle weakness is the main cause of respiratory insufficiency in post-polio patients. Other contributing or causal factors include central hypoventilation due to previous damage from bulbar poliomyelitis,[40] scoliosis and kyphosis, sleep-disordered breathing, obesity, other pulmonary disease, smoking, and cardiac disease.

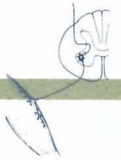
Sleep apnea is a common problem in post-polio patients, and may be central, obstructive, or both.[41] This condition is important to diagnose since, if untreated, it can result in chronic

alveolar hypoventilation, hypoxia, right ventricular strain, cor pulmonale, and even acute cardiopulmonary failure.[42] Patients with symptoms suggestive of sleep apnea, with daytime hypercapnia, or less than 50% of predicted normal supine vital capacity should undergo oxyhemoglobin and PCO_2 monitoring during sleep. If sleep apnea is present, any reversible associated conditions should first be identified and treated. Continuous positive airway pressure (CPAP) is frequently used for treatment.[42]

Patients with pulmonary dysfunction or a history of frequent infections should receive a pneumococcal vaccine at least once and annual influenza vaccinations. Ventilatory assistance may be necessary for those with sleep-disordered breathing or hypoventilation and may result in improvement of symptoms. Non-invasive methods are preferred because of better tolerance by patients and caregivers and lower complication rates.[43] Possibilities include intermittent positive pressure ventilation (IPPV), CPAP, and bilevel positive airway pressure (Bi-PAP). These can be delivered via oral, nasal, or oral/nasal interfaces. Negative pressure ventilators such as the Porta-lung and chest cuirass are also options for some patients, especially during sleep. Glossopharyngeal breathing, a method of projecting a bolus of air into the lungs by using the tongue and pharyngeal muscles, can also be taught to patients. This method of breathing can provide ventilator-free breathing time for some patients who are otherwise ventilator-dependent.[43]

Dysphagia

Symptoms of swallowing dysfunction are less common in post-polio patients than the other difficulties mentioned above, occurring in 10% to 20% of selected samples of post-polio patients.[44] Dysphagia can occur in patients with a previous history of bulbar poliomyelitis, but can also occur in post-polio patients without previous bulbar involvement. In addition, mild to moderate abnormalities may be found on videofluoroscopy whether or not the patient is symptomatic.[45,46] Symptoms can include food sticking, coughing or choking during eating, and slowing of swallowing and eating.[44] Post-polio dysphagia is most commonly due to weakness of pharyngeal or laryngeal muscles. In patients who complain of swallowing or feeding dysfunction, a videofluoroscopic swallowing evaluation should be performed, preferably with a swallowing therapist. Videofluoroscopic abnormalities can include unilateral bolus transport, pooling in the valleculae or pyriform sinuses, delayed pharyngeal constriction, impaired tongue movements, and rarely, aspiration.[45] However, it must not be assumed that all dysphagia in post-polio patients is secondary to polio; other abnormalities such as structural lesions should also be ruled out. In one study,[47] 20 patients with past APP and dysphagia were evaluated with



cinefluoroscopy. Other abnormalities not necessarily secondary to APP were found, including a short stricture (1 patient), a Zenker's diverticulum (1 patient), bilateral pharyngeal pouches (5 patients), and unilateral pouch (1 patient). In addition, laryngeal dysfunction may contribute to dysphagia. In one study,[48] the laryngeal function of 9 of 21 post-polio patients with swallowing complaints was studied; all 9 patients had some degree of abnormality on laryngeal video-stroboscopy. Symptoms of dysphagia and videofluoroscopic abnormalities appear to progress with time.[45,49]

Management of dysphagia (preferably as determined by videofluoroscopy) in a post-polio patient can include changing or restricting the diet to certain "safe" substances such as purées, use of special breathing techniques, use of special swallowing techniques such as turning the head to one side, eating smaller and more frequent meals, and avoiding eating when fatigued.[2,44]

Psychosocial Difficulties

Post-polio patients who are faced with PPS may have great difficulty adjusting to this second and unexpected disability. Many of these patients have had to come to terms with the residual effects of a severe childhood illness, and now they must once again deal with polio-related difficulties. Their problems are compounded by the general lack of knowledge in the medical profession about both APP and PPS.[50]

Some investigators have described a "polio personality" and have suggested that this may actually contribute to post-polio sequelae.[51,52] Polio survivors tend to be well-educated, competent, hard-driving individuals who demand perfection both from themselves and from those around them.[2,53] In a survey conducted by Bruno and Frick,[51] 676 polio survivors were recruited by sending out 1200 questionnaires to post-polio clinics and support groups in the United States. The mean type A score was found to be significantly higher in this post-polio group than in a previously reported non-disabled control group. In addition, type A score was significantly higher in those with muscle pain and fatigue. Despite their difficulties, the surveyed polio survivors have more years of formal education and a larger proportion are married than the general disabled and non-disabled populations. They also have higher levels of employment than the general disabled population.[53]

Frick[50] suggested that individuals with PPS may experience personal devaluation, isolation, and depression as psychologic responses. In one study,[54] the Symptom Check List-90R (SCL-90R), Psychosocial Adjustment to Illness Scale–Self Report (PAIS-SR), and questionnaire

about polio histories were administered to 93 individuals with a history of APP (71 from a post-polio clinic and 22 recruited from a post-polio support group). Results indicated psychologic distress. Elevated SCL-90R scores occurred in men for somatization, depression, anxiety, hostility, and phobia. In women, elevated scores occurred for somatization, depression, anxiety, and psychoticism. In another study,[55] in which 116 APP survivors were recruited from a polio registry, the prevalence of depression and distress was found to be 15.8%. Psychologic distress/depression was correlated with physical symptoms. The emotional responses to a new disability may pose difficulties for the treatment of these patients. Patients may resist making the necessary changes in their life to effectively manage their new difficulties. Yet, those who do comply with clinical recommendations achieve more favorable outcomes in terms of symptoms and muscle function.[56]

Treatment of psychosocial difficulties related to PPS is best managed with an interdisciplinary approach. It may include obtaining help from a post-polio support group and evaluation and treatment by health professionals such as social workers, psychologists, and psychiatrists.

Drug Trials and Pharmacotherapy

Several small clinical trials of pharmacologic treatments have been completed in PPS patients. Pyridostigmine (Mestinon) 180 mg per day has been evaluated by Trojan et al[57] in an open trial using an objective measure of neuromuscular junction transmission (stimulation SFEMG) in 17 patients. A significant relation between subjective fatigue response to pyridostigmine and improvement in neuromuscular transmission with edrophonium (a short-acting anticholinesterase similar to pyridostigmine) was found. In addition, Seizert and coworkers[58] have found improvements in some objective measures of strength and subjective measures of fatigue with pyridostigmine 180 mg per day in a double-blind, placebo-controlled, crossover trial in 27 PPS patients.

Stein et al[59] randomly assigned 25 PPS patients with fatigue to amantadine 100 mg twice a day or to placebo for 6 weeks. Fatigue level was assessed with the Fatigue Severity Scale and Visual Analog Scale for Fatigue. No association was found between amantadine and clinical response to fatigue, although 54% of amantadine patients and 43% of placebo patients reported improvement in fatigue. Dinsmore et al[60] studied the effect of high-dose prednisone in 17 PPS patients (with new muscle weakness). Patients were randomly assigned either to prednisone (80 mg per day for 28 days, followed by a gradual reduction) or placebo. Outcome assessments included measures of isometric strength by a modified Tufts Quantitative Neuromuscular

Examination (TQNE),[61] manual muscle testing, and subjective fatigue assessment. There were no significant differences between groups in terms of muscle strength and subjective fatigue. Another medication that may warrant further study is deprenyl (selegiline). In a report of two cases[62] deprenyl was found to produce an improvement in PPS symptoms, and this improvement ceased with discontinuation of the drug.

In conclusion, several potential pharmacologic treatments have been evaluated in PPS, and thus far pyridostigmine appears to be the most promising.

REFERENCES

1. Agre JC, Rodriquez AA, Sperling KB. Symptoms and clinical impressions of patients seen in a postpolio clinic. *Arch Phys Med Rehab* 1989;70:367-370.
2. Gawne AC, Halstead LS. Post-polio syndrome: pathophysiology and clinical management. *Crit Rev Phys Rehab Med* 1995;7:147-188.
3. Bennett RL, Knowlton GC. Overwork weakness in partially denervated skeletal muscle. *Clin Orthopedics* 1958;12:22-29.
4. Jubelt B, Cashman NR. Neurological manifestations of the post-polio syndrome. *CRC Crit Rev Neurobiol* 1987;3:199-220.
5. Herbison GJ, Jaweed MM, Ditunno JF, Scott CM. Effect of overwork during reinnervation of rat muscle. *Exp Neurol* 1973;41:1-14.
6. Herbison GJ, Jaweed MM, Ditunno JF. Effect of swimming on reinnervation of rat skeletal muscle. *J Neurol Neurosurg Psychiatry* 1974;37:1247-1251.
7. Herbison GJ, Jaweed MM, Ditunno JF. Strengthening exercises in normal muscle. In: Halstead LS, Wiechers DO, eds. *Late Effects of Poliomyelitis*. Miami, FL: Symposia Foundation, 1985:163-169.
8. Jaweed MM, Herbison GJ, Ditunno JF. Effect of overwork weakness on isometric tension development during peripheral reinnervation of rat soleus [Abstract]. *Fed Proc* 1984;43:1016.
9. Feldman RM. Late effects of poliomyelitis: clinical pathophysiology. In: Halstead LS, Wiechers DO, eds. *Late Effects of Poliomyelitis*. Miami, FL: Symposia Foundation. 1985:109-117.
10. Feldman RM, Soskolne CL. The use of non-fatiguing strengthening exercises in post-polio syndrome. In: Halstead LS, Weichers DO, eds. *Research and Clinical Aspects of the Late Effects of Poliomyelitis*. White Plains, NY: March of Dimes Birth Defects Foundation, 1987:335-341.
11. Einarsson G, Grimby G. Strengthening exercise program in post-polio subjects. In: Halstead LS, Wiechers DO, eds. *Research and Clinical Aspects of the Late Effects of Poliomyelitis*. White Plains, NY: March of Dimes Birth Defects Foundation, 1987:275-283.
12. Einarsson G. Muscle conditioning in late poliomyelitis. *Arch Phys Med Rehab* 1991;72:11-14.
13. Fillyaw MJ, Badger GJ, Goodwin GD, Bradley WG, Fries TJ, Shukla A. The effects of long-term non-fatiguing resistance exercise in subjects with post-polio syndrome. *Orthopedics* 1991;14:1253-1256.

14. Agre JC, Rodriquez AA, Harmon RL, Swiggum ER, Franke TM. Strengthening exercise can improve function in post-polio subjects without detectable adverse affect upon the surviving motor units or muscle [Abstract]. *Arch Phys Med Rehab* 1995;76:1036.

15. Jones DR, Speier J, Canine K, Owen R, Stull GA. Cardiorespiratory responses to aerobic training by patients with postpoliomyelitis sequelae. *JAMA* 1989;261:3255-3258.

16. Owen RR, Jones D. Polio residuals clinic: conditioning exercise program. *Orthopedics* 1985;8:882-883.

17. Kriz JL, Jones DR, Speier JL, Canine JK, Owen RR, Serfass RC. Cardiorespiratory responses to upper extremity aerobic training by post-polio subjects. *Arch Phys Med Rehabil* 1992;73:49-54.

18. Dean E, Ross J. Effect of modified aerobic training on movement energetics in polio survivors. *Orthopedics* 1991;14:1243-1246.

19. Agre JC. The role of exercise in the patient with post-polio syndrome. *Ann NY Acad Sci* 1995;753:321-334.

20. Perry J, Barnes G, Gronley JK. The postpolio syndrome. *Clin Orthop Rel Res* 1988;233:145-162.

21. Waring WP, McLaurin TM. Correlation of creatine kinase and gait measurement in the postpolio population: a corrected version. *Arch Phys Med Rehab* 1992;73:447-450.

22. Peach PE. Overwork weakness with evidence of muscle damage in a patient with residual paralysis from polio. *Arch Phys Med Rehab* 1990;71:248-250.

23. Waring WP, Maynard F, Grady W, Grady R, Boyles C. Influence of appropriate lower extremity orthotic management on ambulation, pain, and fatigue in a postpolio population. *Arch Phys Med Rehab*. 1989;70:371-375.

24. Clark DR, Perry J, Lunsford TR. Case studies – orthotic management of the adult post-polio patient. *Orthotics Prosthetics* 1986;40:43-50.

25. Agre JC, Rodriquez AA. Intermittent isometric activity: its effect on muscle fatigue in postpolio subjects. *Arch Phys Med Rehab* 1991;72:971-975.

26. Smith LK, McDermott K. Pain in post-poliomyelitis: addressing causes versus treating effects. In: Halstead LS, Wiechers DO, eds. *Research and Clinical Aspects of the Late Effects of Poliomyelitis*. White Plains, NY: March of Dimes Birth Defects Foundation, 1987:121-134.

27. Trojan DA, Cashman NR. Fibromyalgia is common in a postpoliomyelitis clinic. *Arch Neurol* 1995;52:620-624.

28. Werner RA, Waring W, Maynard F. Osteoarthritis of the hand and wrist in the post-poliomyelitis population. *Arch Phys Med Rehab* 1992;73:1069-1072.

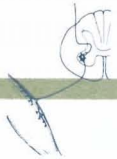
29. Perry J, Mulroy SJ, Renwick SE. The relationship of lower extremity strength and gait parameters in patients with post-polio syndrome. *Arch Phys Med Rehab* 1993;74:165-169.

30. Perry J, Fontaine JD, Mulroy S. Findings in post-poliomyelitis syndrome. *J Bone Joint Surg* 1995;77-A:1148-1153.

31. Gawne AC, Pham BT, Halstead LS. Electrodiagnostic findings in 108 consecutive patients referred to a post-polio clinic. *Ann NY Acad of Sci* 1995;753:383-385.

32. Werner RA, Waring W, Davidoff G. Risk factors for median mononeuropathy of the wrist in postpoliomyelitis patients. *Arch Phys Med Rehab* 1989;70:464-467.

33. Kruger VL, Kraft GH, Deitz JC, Ameis A, Polissar L. Carpal tunnel syndrome: objective measures and splint use. *Arch Phys Med Rehab* 1991;72:517-520.



34. Halstead LS, Wiechers DO, Rossi CD. Late effects of poliomyelitis: a national survey. In: Halstead LS, Wiechers DO, eds. *Late Effects of Poliomyelitis*. Miami, FL: Symposia Foundation, 1985:11-31.

35. Dean E, Ross J, Road JD, Courtenay L, Madill KJ. Pulmonary function in individuals with a history of poliomyelitis. *Chest* 1991;100:118-128.

36. Blomstrand A, Bake B. Post-polio lung function. *Scand J Rehab Med* 1992;24:43-49.

37. Bach JR, Alba AS. Pulmonary dysfunction and sleep disordered breathing as post-polio sequelae: evaluation and management. *Orthopedics* 1991;14:1329-1337.

38. Fischer DA. Poliomyelitis: late respiratory complications and management. *Orthopedics* 1985;8:891-894.

39. Bach JR, Alba AS, Bohatiuk G, Saporito L, Lee M. Mouth intermittent positive pressure ventilation in the management of postpolio respiratory insufficiency. *Chest* 1987;91:859-864.

40. Plum F, Swanson AG. Central neurogenic hyperventilation in man. *Arch Neurol Psychiatry* 1959;81:535-547.

41. Steljes DG, Kryger MH, Kirk BW, Millar TW. Sleep in postpolio syndrome. *Chest* 1990;98:133-140.

42. Bach JR. Evaluation and management of post-polio respiratory sequelae: noninvasive options. In: Halstead LS, Grimby G, eds. *Post-polio Syndrome*. Philadelphia: Hanley & Belfus, 1995,89-111.

43. Bach JR. Management of post-polio respiratory sequelae. *Ann NY Acad of Sci* 1995;753:96-102.

44. Buchholz DW, Jones B. Post-polio dysphagia: alarm or caution? *Orthopedics* 1991;14:1303-1305.

45. Sonies BC, Dalakas MC. Dysphagia in patients with the post-polio syndrome. *N Engl J Med* 1991;324:1162-1167.

46. Sonies BC. Long-term effects of post-polio on oral-motor and swallowing function. In: Halstead LS, Grimby G, eds. *Post-polio Syndrome*. Philadelphia: Hanley & Belfus, 1995:125-140.

47. Jones B, Buchholz DW, Ravich WJ, Donner MW. Swallowing dysfunction in the postpolio syndrome: a cinefluorographic study. *AJR* 1992;158:283-286.

48. Driscoll BP, Gracco C, Coelho C, Goldstein J, Oshima K, Tierney E, Sasaki CT. Laryngeal function in postpolio patients. *Laryngoscope* 1995;105:35-41.

49. Sonies BC, Dalakas MC. Progression of oral-motor and swallowing symptoms in the post-polio syndrome. *Ann NY Acad Sci* 1995;753:87-95.

50. Frick NM. Post-polio sequelae and the psychology of second disability. *Orthopedics* 1985;8:851-856.

51. Bruno RL, Frick NM. Stress and "type A" behavior as precipitants of post-polio sequelae: the Felician/Columbia Survey. In: Halstead LS, Wiechers DO, eds. *Research and Clinical Aspects of the Late Effects of Poliomyelitis*. White Plains, NY: March Of Dimes Birth Defects Foundation, 1987:145-155.

52. Bruno RL, Frick NM, Cohen J. Polioencephalitis, stress, and the etiology of post-polio sequelae. *Orthopedics* 1991;14:1269-1276.

53. Bruno RL, Frick NM. The psychology of polio as prelude to post-polio sequelae: behavior modification and psychotherapy. *Orthopedics* 1991;14:1185-1193.

54. Conrady LJ, Wish JR, Agre JC, Rodriquez AA, Sperling KB. Psychologic characteristics of polio survivors: a preliminary report. *Arch Phys Med Rehab* 1989;70:458-468.

55. Tate DG, Forchheimer M, Kirsch N, Maynard F, Roller A. Prevalence and associated features of depression and psychological distress in polio survivors. *Arch Phys Med Rehab* 1993;74:1056-1060.

56. Peach PE, Olejnik S. Post-polio sequelae: effect of treatment and noncompliance on post-polio sequelae. *Orthopedics* 1991;14:1199-1203.

57. Trojan DA, Gendron D, Cashman NR. Anticholinesterase-responsive neuromuscular junction transmission defects in post-poliomyelitis fatigue. *J Neurol Sci* 1993;114:170-177.

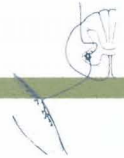
58. Seizert BP, Speier JL, Canine JK. Pyridostigmine effect on strength, endurance, and fatigue in post-polio patients [Abstract]. *Arch Phys Med Rehab* 1994;75:1049.

59. Stein DP, Dambrosia JM, Dalakas MC. A double-blind, placebo-controlled trial of amantadine for the treatment of fatigue in patients with the post-polio syndrome. *Ann NY Acad Sci* 1995;753:296-302.

60. Dinsmore S, Dambrosia J, Dalakas MC. A double-blind, placebo-controlled trial of high-dose prednisone for the treatment of post-poliomeylitis syndrome. *Ann NY Acad Sci* 1995;753:303-313.

61. Andres PL, Hedlund W, Finison L, Conlon T, Felmus M, Munset TL. Quantitative motor assessment in amyotrophic lateral sclerosis. *Neurology* 1986;36:937-941.

62. Bamford CR, Montgomery Jr EB, Munoz JE, Stumpf C, Pry S. Postpolio syndrome: response to deprenyl (selegiline). *Int J Neurosci* 1993;71:183-188.



Chapter 6

Future Approaches to Post-poliomyelitis Syndrome

Introduction

If post-poliomyelitis syndrome (PPS) weakness, fatigue, and fatiguability are due to degeneration and dysfunction of motor axonal sprouts (see Chapter 3), future treatments based on support of the integrity and/or function of terminal axons may improve or delay PPS symptoms. However, the state of our knowledge regarding the cause of the degeneration limits our ability to identify appropriate therapies. Thus, for example, if reactive oxygen species are implicated in terminal axonal dysfunction, could neuroprotective agents such as selegiline, vitamin E, or lazeroids inhibit degeneration? A number of trophic factors have been found to display activity in the survival and/or function of components of the motor unit, including terminal axons: insulin-like growth factor-1 (IGF-1), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT3), neurotrophin 4/5 (NT4/5), and glial-derived growth factor (GDNF). Several of these factors are being tested in amyotrophic lateral sclerosis (ALS) and other motor neuron diseases. Agents in this group that prove to be safe and effective in the treatment of fulminantly progressive ALS are obvious candidates for the indolently progressive PPS. Other "small molecule" growth factor mimics and neuroprotective agents may be considered in the future.

Treatment of Terminal Axonal Dysfunction

Pyridostigmine is an anticholinesterase that inhibits the hydrolysis of acetylcholine, thereby prolonging its survival and effect in the neuromuscular junction (NMJ) and selected central synapses. Pyridostigmine has been widely used for the treatment of fatiguability in myasthenia gravis. In view of the NMJ transmission dysfunction observed in PPS, pyridostigmine has also been suggested as a treatment for this disorder.[1-6] In an open trial of pyridostigmine 180 mg/day, 59% of 27 patients noted an improvement in fatigue with the medication and requested continuation of the treatment.[5,6] Preliminary results from a crossover trial of pyridostigmine in 27 PPS patients showed that for some measures (subjective assessments of fatigue, objective assessments of strength in the upper extremities), the improvement over baseline was significant.[4]

It is possible that pyridostigmine has at least three beneficial effects on PPS motor units:

1. *Acute improvement of fatigue and fatiguability by amelioration of NMJ transmission defects.*

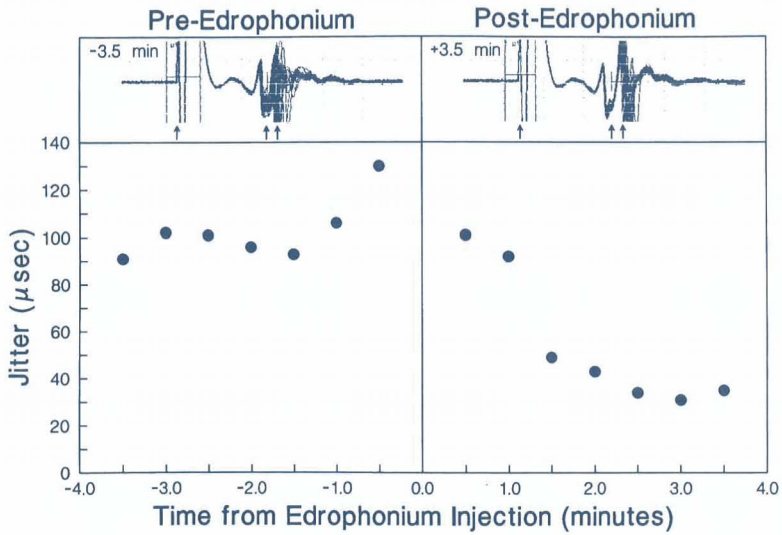


Figure 1. Pre- and post-edrophonium jitter as determined by stimulation single-fiber electromyography (S-SFEMG) in the vastus medialis muscle of a pyridostigmine responder. Upper panels show examples of raw data; the numerical jitter value is determined by the mean consecutive difference between the stimulation artifact (single arrows) and the unstable potential (double arrows) in 50 superimposed stimulations. Jitter means (lower panels) were recorded every 30 sec 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 μsec SEM) significantly differed from mean jitter for the 5 min after edrophonium (47.6 ± 8.41 μsec, $T = 4.65$, $p<0.0001$). Thus, this subject was judged to have a significant reduction in jitter with edrophonium in the studied unstable potential. Reprinted from *Journal of Neurological Sciences*, volume 114. Trojan DA, Gendron D, Cashman NR. Anticholinesterase-responsive neuromuscular junction transmission defects in post-poliomyelitis fatigue, pages 170-177, 1993, with kind permission of Elsevier Science–NL, Sara Burgerhardstraat 25, 1055 KV Amsterdam, The Netherlands.

Subjects with antecedent acute paralytic poliomyelitis (APP) show defects in NMJ transmission by repetitive stimulation[7] and on single-fiber electromyography (SFEMG).[2,8-10] Defects in NMJ transmission in PPS can be partially overcome with parenteral cholinesterase inhibitors such as neostigmine[7] and edrophonium[3] (see Figure 1) and by oral pyridostigmine.[11] Patients administered pyridostigmine report decreased muscle fatiguability and decreased generalized fatigue,[3-6] consistent with an immediate cholinergic effect on NMJ transmission.

2. *Acute improvement of strength by recruitment of blocked or defective neuromuscular junctions.* Subjects with prior APP show blocking with SFEMG, which can be partially reversed by oral pyridostigmine.[11] Oral pyridostigmine can improve strength acutely, consistent with recruitment of dysfunctional NMJs.[4,12] It is possible that this acute mechanism of pyridostigmine is responsible for some of the increased strength and endurance reported by subjects administered this agent.

3. *Chronic improvement of muscle bulk and strength, and axonal sprout maintenance, by "trophic effects."* Subjects with past APP (including those with PPS) have been shown to have decreased IGF-1 due to an early and inappropriate "growth hormone menopause."[13,14] Because IGF-1 promotes synthesis of protein and nucleic acid in muscle cells and sprouting of peripheral motor axons,[15] it is possible that loss of IGF-1 is responsible for axonal degeneration and muscle weakness in PPS. Pyridostigmine increases growth hormone (GH) secretion and subsequent circulating IGF-1 levels.[16,17] It is thus possible that chronic effects of pyridostigmine may be due to cholinergic modulation of the GH-IGF-1 axis. Other potential "trophic" effects of pyridostigmine include an acetylcholine effect on partially denervated PPS muscle[18,19] and induction of calcitonin gene-related peptide (CGRP) secretion.[20]

NAPPS to Evaluate Safety and Efficacy

In view of the preliminary efficacy data and the rationale detailed above, the North American Postpoliomyelitis Pyridostigmine Study (NAPPS) was organized. NAPPS will conduct a multicenter, randomized, double-blind, placebo-controlled, therapeutic trial of Mestinon (pyridostigmine) in PPS, using the pyridostigmine dosage (60 mg three times per day) previously found to be effective in several small clinical trials.[3-6,10] The primary objective will be to determine the clinical efficacy of a 6-month course of pyridostigmine in PPS by evaluating its effect on the short form health survey (SF-36)[21] physical functioning scale. Secondary objectives will be (1) to determine the effect of pyridostigmine in PPS on isometric strength as measured by a modified Tufts quantitative neuromuscular exam;[22-24] (2) to determine the effect of pyridostig-

mine in PPS on selected subjective scales including the Hare fatigue symptom scale,[25] the fatigue severity scale,[26] and general health status as measured by the remaining scales of the SF-36; (3) to determine the effect of pyridostigmine in PPS on circulating IGF-1 levels; and (4) to determine the incidence and severity of side effects from pyridostigmine in PPS.

Although pyridostigmine has been in wide use as an approved drug for myasthenia gravis for decades, anticholinesterases are known to be associated with acute and chronic toxicities in experimental animals and in humans.[27] However, the dosages used in those studies are many times higher than the dosage to be used in the NAPPS study and previous studies of pyridostigmine in PPS (2 g per day in myasthenia gravis vs 180 mg per day in PPS). In two previous studies utilizing this "low dosage" pyridostigmine regimen for PPS,[3,4,10] acute adverse events were observed in approximately 50% of PPS individuals and included increased gut motility (loose stool and occasional intestinal cramps), blurred vision, increased urinary frequency, muscle cramps, and fasciculations. All these adverse events tended to decrease with chronic use of the medication.[5,6] Increased muscle weakness has been observed as a consequence of pyridostigmine overdose in myasthenia gravis, and it can also occur rarely in PPS patients.[5] Increased muscle weakness is reversible on cessation of pyridostigmine administration. Pyridostigmine 90 mg per day was recently used in 41,650 soldiers in the Gulf War as a pretreatment of possible organophosphate intoxication. In a retrospective study, 50% of soldiers complained of mild side effects (similar to those noted above), but <0.1% discontinued the medication because of side effects.[28] Pyridostigmine did not affect soldiers' ability to perform.[29] Studies have shown that pyridostigmine at 90 mg per day has no effect on aviators' visual ability,[30] on pilot performance,[31] on physiologic responses to moderate exercise-heat stress,[32] and on nonspecific bronchial hyperreactivity in normal non-smokers, smokers, and mild asthmatics.[33]

Research into the causes and treatment of PPS is being conducted at a rapidly accelerating pace, providing hope to the thousands suffering from its symptoms.

REFERENCES

1. Cashman, In: Raymond CA. Decades after polio epidemics, survivors report new symptoms. *JAMA* 1986;255:1397-1404.
2. Cashman NR, Maselli R, Wollman RL, Roos R, Simon R, Antel J. Late denervation in patients with antecedent paralytic poliomyelitis. *N Engl J Med* 1987;317:7-12.
3. Trojan DA, Gendron D, Cashman NR. Anticholinesterase-responsive neuromuscular junction transmission defects in post-poliomyelitis fatigue. *J Neurol Sci* 1993;114:170-177.
4. Seizert BP, Speier JL, Canine K. Pyridostigmine effect on strength, endurance and fatigue in post-polio patients [Abstract]. *Arch Phys Med Rehab* 1994;75:1049.
5. Trojan DA, Cashman NR. An open trial of pyridostigmine in postpoliomyelitis syndrome. *Can J Neurol Sci* 1995;22:223-227.
6. Trojan DA, Cashman NR. Anticholinesterases in post-poliomyelitis syndrome. *Ann NY Acad Sci* 1995;753:285-295.
7. Hodes R. Electromyographic study of defects of neuromuscular transmission in human poliomyelitis. *Arch Neurol Psychiatry* 1948;60:457-473.
8. Wiechers DO, Hubell SL. Late changes of the motor unit after acute poliomyelitis. *Muscle Nerve* 1981;4:524-528.
9. Dalakas MC, Elder C, Hallet M, et al. A long-term follow-up study of patients with post-poliomyelitis neuromuscular symptoms. *N Engl J Med* 1986;314:959-963.
10. Trojan DA, Gendron D, Cashman NR. Stimulation frequency-dependent neuromuscular junction transmission defects in patients with prior poliomyelitis. *J Neurol Sci* 1993;118:150-157.
11. Girlanda P, Venuto C, Mangiapane R, Nicolosi C, Messina C. Effect of anticholinesterase agents on late progressive weakness after poliomyelitis: a single fibre EMG study [Abstract]. *Neurology* 1989;Suppl37:164.
12. Kilfoil MR, St. Pierre DMM, Trojan DA, Cashman NR. The effects of pyridostigmine (Mestinon) on isokinetic evaluation of fatigue in subjects with post-poliomyelitis syndrome [Abstract]. *Phys Ther* 1992;72:S112.
13. Shetty KR, Mattson DE, Rudman IW, Rudman D. Hyposomatomedinemia in men with poliomyelitis syndrome. *J Am Geriatr Soc* 1991;39:185-191.
14. Rao U, Shetty KR, Mattson DE, Rudman IW, Rudman D. Prevalence of low plasma IGF-1 in poliomyelitis survivors. *J Am Geriatr Soc* 1993;41:697-702.
15. Yu E, Callison K, Roberts-Lewis JM, Grebow P. The effect of insulin-like growth factor-1 on the neuromuscular junction in adult rat skeletal muscle. *Soc Neurosci Abstr* 1991;17:225.
16. Ghigo E, Goffi S, Arvat E, et al. Pyridostigmine partially restores the GH responsiveness to GHRH in normal aging. *Acta Endocrinol* (Copenh) 1990;123:169-174.
17. Arvat E, Cappa M, Casanueva FF, Dieguez C, Ghigo E, Nicolosi M, Valcavi R, Zini M. Pyridostigmine potentiates growth hormone (GH)-releasing hormone-induced GH release in both men and women. *J Clin Endocrinol Metab* 1993;76:374-377.
18. Drachman DB. The role of acetylcholine as a neurotrophic transmitter. In: *Trophic Functions of the Neuron*. Annals of the New York Academy of Sciences, 1974.
19. Miller RG. The effects of nerve injury on the neuromuscular junction. In: Bruback RA, Gerst J, eds. *Neuromuscular Junction*. Mount Kisco, NY: Futura Publishing Co, 1984;203-255.

20. Trasforini G, Margutti A, Vergnani L, et al. Evidence that enhancement of cholinergic tone increases basal plasma levels of calcitonin gene-related peptide in normal man. *J Clin Endocrinol Metab* 1994;78:763-766.

21. Ware JE, Snow KK, Kosinski M, Gandek B. *The SF-36 Health Survey: Manual and Interpretation Guide*. Boston: Nimrod Press, 1993.

22. Andres PL, Hedlund W, Finison L, Conlon T, Felmus M, Munsat TL. Quantitative motor assessment in amyotrophic lateral sclerosis. *Neurology* 1986;36:937-941.

23. Andres P, Skerry L, Munsat T. Measurement of strength in neuromuscular disease. In: Munsat T, ed. *Quantification of Neurologic Deficit*. Boston: Butterworth, 1989:87-100.

24. Finkelman R, Munsat T, Andres BT, Brussock C. Alterations of strength in post-polio syndrome. In: Munsat TL, ed. *Post-polio Syndrome*. Boston: Butterworth, 1991:91-103.

25. Hare TW, Hakki AH, Lowenthal DT, Iskandrian AS, Segal BL. Simplified scale for rating perceived exertion in patients with coronary artery disease. *Ann Sports Med* 1985;2:64-68.

26. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. *Arch Neurol* 1989;46:1121-1123.

27. Munsat TL. Anticholinesterase abuse in myasthenia gravis. *J Neurol Sci* 1984;64:5-10.

28. Keeler JR, Hurst CG, Dunn MA. Pyridostigmine used as a nerve agent pretreatment under wartime conditions. *JAMA* 1991;266:693-695.

29. Cook JE, Kolka MA, Wenger CB. Chronic pyridostigmine bromide administration: side effects among soldiers working in a desert environment. *Mil Med* 1992;157:250-254.

30. Wiley RW, Kotulak JC, Behar I. The effects of pyridostigmine bromide on visual performance. *Aviat Space Environ Med* 1992;63:1054-1059.

31. Izraeli S, Avgar D, Almog S, et al. The effect of repeated doses of 30 mg pyridostigmine bromide on pilot performance in an A-4 flight simulator. *Aviat Space Environ Med* 1990;61:430-432.

32. Wenger CB, Latzka WA. Effects of pyridostigmine bromide on physiological responses to heat, exercise, and hypohydration. *Aviat Space Environ Med* 1992;63:37-45.

33. Roach JM, Eliasson AH, Phillips YY. The effect of pyridostigmine on bronchial hyperreactivity. *Chest* 1993;103:1755-1758.