Pathophysiology and diagnosis of post-polio syndrome

Daria A. Trojan*, Neil R. Cashman

Department of Neurology and Neurosurgery
Montreal Neurological Institute and Hospital
McGill University
Montreal, Quebec, Canada

ELSEVIER

NeuroRehabilitation
An Interdisciplinary Journal

NeuroRehabilitation 8 (1997) 83-92

Abstract

Post-poliomyelitis syndrome is defined as a clinical syndrome of new weakness, fatigue and pain which can occur several decades following recovery from paralytic poliomyelitis. The cause of this disorder is still unclear, and many possible etiologies have been proposed. The most widely accepted etiology was first proposed by Wiechers and Hubbell, which attributes PPS to a distal degeneration of massively enlarged post-polio motor units. Other probable contributing factors to the onset of this disease are the ageing process, and overuse. Currently, there is no specific diagnostic test for PPS, which continues to be a diagnosis of exclusion in an individual with symptoms and signs of the disorder. © 1997 Elsevier Science Ireland Ltd.

Keywords: Poliomyelitis; Diagnosis; Pathophysiology

*Corresponding author. Tel.: + 1 514 3988911; fax: +1 514 3987371.

PII S 1053-8135(96)002 1 3-2

1. Introduction

Post-polio syndrome (PPS) is the term most commonly used to describe the new difficulties which may occur many years after recovery from paralytic poliomyelitis *[1-7]*. Although many symptoms may be reported by these patients, the most commonly reported are new weakness, fatigue, and pain. Therefore, these three symptoms have been used to define PPS. This article will concentrate on the symptoms of new

weakness and fatigue, because these symptoms are most likely referable to the motor unit. Currently, it is unclear how the symptom of pain, which is uncommmon in the classical motor unit diseases such as amyotrophic lateral sclerosis, is related to disease of the motor unit.

Although the definitive etiology of PPS (new weakness, fatigue) is unclear, a consensus as to the most likely cause is beginning to emerge. Jubelt and Cashman *[4]* reviewed nine possible causes of PPS. These included (1) chronic poliovirus infection, (2) death of remaining motor neurons with the normal ageing process, (3) premature ageing of cells permanently damaged by poliovirus, (4) premature ageing of remaining normal motor neurons due to an increased metabolic demand, (5) loss of muscle fibers in enlarged, reinnervated motor units with age, (6) predisposition to motor neuron degeneration because of glial, vascular, and lymphatic damage caused by poliovirus, (7) poliomyelitis-induced vulnerability of motor neurons to secondary insults, (8) genetic predisposition of motor neurons to both poliomyelitis and premature degeneration, and (9) an immune-mediated mechanism. The most likely possiblity, that of a peripheral disintegration of enlarged post-polio motor units, which was first proposed by Wiechers and Hubbell *[8]*, will be discussed in greatest detail.

The normal ageing process which is associated with a gradual dropout of motor units *[4,9-11]* and other changes such as growth hormone and insulin-like growth factor-1 (IGF-1) deficiency *[12-16]* is most likely a contributing factor. Overuse *[17,18]* and conversely disuse *[19]* are other probable contributing factors for the development of PPS. Still uncertain is the significance of poliovirus genome fragments detected in cerebrospinal fluid of PPS patients *[20-27]*, and the role of immune mechanisms *[3,28-31]*.

2. Peripheral disintegration of enlarged post-polio motor units and new weakness in PPS

Acute paralytic polio involves motor neuron invasion by poliovirus, and is primarily a disease of the motor unit (defined as a motor neuron together with all the muscle fibers that it innervates). Pathological studies have revealed that poliovirus can also produce lesions 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 *[32,33]*. During acute polio, motor neuron invasion can result either in cell death or injury as shown in Fig. 1 *[4,32]*. Motor neuron death will cause denervation of the muscle fibers it supplies, which may produce clinical weakness. Pathological studies have revealed that in limbs with minimal paralysis or normal function, up to 20% of the motor neurons could be destroyed *[34]*. During the recovery process following acute polio, remaining brainstem and spinal cord motor neurons can elaborate new branches, or axonal sprouts. Sprouts can form from three areas of a motor neuron; from the terminal axon, from the proximal unmyelinated axon, or from the more proximal nodes of Ranvier. These sprouts can reinnervate muscle fibers which have lost their innervation due to acute polio (Fig. 1). Sprouting can restore the capacity of voluntary muscle fiber contraction, and thus improve clinical strength. In addition to sprouting, muscle fiber hypertrophy of innervated muscle can contribute to the recovery of strength after paralytic polio.

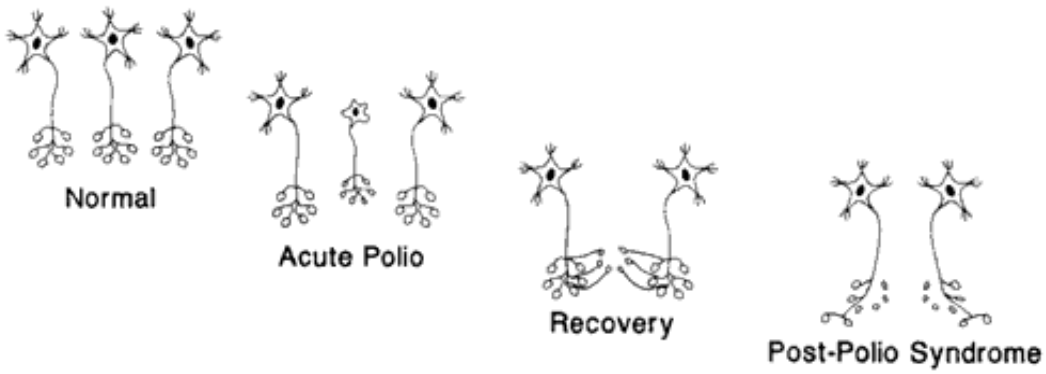

Fig. 1. Normal: Three normal motor units are illustrated. Acute Polio: Poliovirus invasion of one motor neuron produces degeneration of the motor neuron with denervation of muscle fibers innervated by that neuron. Recovery: Recovery following paralytic polio occurs by local sprouting from surviving motor neurons with reinnervation of some or all muscle fibers. Recovery may also involve muscle fiber hypertrophy (not illustrated). Post-polio syndrome: A distal degeneration of enlarged post-polio motor units with denervation of muscle fibers is believed to be the most likely cause of post-polio syndrome.
This figure is reprinted with permission from Milestone Medical Communications, A Division of Ruder-Finn, from a disease management monograph entitled 'Current Trends in Post-Poliomyelitis Syndrome' (1996).

Motor neuron sprouting produces at least two changes in a motor unit. First, sprouting increases motor unit size. Muscle biopsy studies have shown that after recovery from acute paralytic polio, motor neurons may be innervating up to eight times the number of muscle fibers they would normally supply *[35]*. Other studies have shown that even with a loss of 50% of motor neurons supplying a particular muscle, sprouting can achieve complete reinnervation with normal muscle strength *[36]*. Second, motor neuron sprouting can produce fiber type grouping. There are at least three histochemical muscle fiber types, which in a normal muscle are distributed in a 'mosaic' pattern throughout a muscle fascicle. The histochemical type of a muscle fiber is determined by the motor neuron by which it is innervated. Thus, local motor neuron sprouting will produce a grouping of histochemically similar muscle fiber types.

Wiechers and Hubbell *[8,37]* have proposed that these abnormally enlarged motor units after acute paralytic polio are not indefinitely stable, but that terminal axonal sprouts degenerate over time producing denervation of muscle fibers (Fig. 1). It is possible that some of these denervated muscle fibers may become reinnervated by sprouts from neighboring motor neurons, producing a continuous 'remodeling' process of the post-polio motor units. However, some of these muscle fibers will become permanently denervated, producing a gradual denervation with increasing weakness. The investigators also demonstrated that jitter on single fiber electromyography (SFEMG; a measure of neuromuscular junction function and thus terminal axonal integrity in polio muscles) increased with time since acute polio. Even though no other investigators have been able to reproduce these results, the theory based on these findings has been upheld by other studies.

Muscle biopsy studies probably provide the best evidence for the Wiechers and Hubbell hypothesis. A muscle fiber that has lost its innervation for a few weeks' time can display fiber atrophy and is termed an angular atrophic fiber on muscle biopsy. If the fiber remains denervated for months, it becomes a tiny 'nuclear bag.' Post-polio muscles on biopsy contain isolated angular atrophic fibers which were most likely denervated a few weeks prior to the biopsy. In addition, many extremely atrophic nuclear bags are found, some of which may be present from the original illness. The finding of isolated atrophic fibers suggests degeneration of terminal axons, as hypothesized by Wiechers and Hubbell. If PPS were a motor neuron disease (such as amyotrophic lateral sclerosis), then it would be expected that the muscle fibers of entire motor units would become simultaneously denervated. Even though some group atrophy is found on post-polio muscle biopsies, the predominant finding is scattered fiber atrophy. Because of these findings, new weakness in PPS is most likely due to degeneration of terminal axons, and not to death of motor neurons.

Despite the above findings, there are some difficulties with this hypothesis. Evidence for denervation (both on muscle biopsy and electromyography studies), occurs both in patients with past polio who are

noting new weakness, and in patients with past polio without new weakness [38]. In addition, a specialized electrophysiologic technique, macro-electromyography (macro-EMG; which can estimate motor unit size) does not reproducibly detect a gradual decline in motor unit size. In one study [39], macro motor unit potential amplitudes were found to be smaller in post-polio muscles with new weakness and atrophy than in post-polio muscles of normal strength or in weak but stable post-polio muscles. This would be consistent with the Wiechers-Hubbell hypothesis. In another study where macro-EMG was performed prospectively on subjects, motor unit size actually appeared to increase over time after acute polio [40].

3. Neuromuscular junction defects and muscle fatiguability in PPS

Fatigue in PPS is probably the major and most disabling symptom in PPS [2,41]. It can be either general or muscular, but frequently both occur concurrently. General fatigue is usually described as a 'flu-like' exhaustion, and is typically worse with physical activity and later in the day. Manifestations can include an increased sleep requirement, naps during the day, and decreased concentration. Muscle fatigue (or muscle fatiguability) is defined as increased muscle weakness with exertion, which improves with rest. However, when PPS patients have been compared to controls, the symptom of general fatigue occurred with a similar frequency in both groups, but muscle fatigue occurred significantly more commonly in PPS [42]. Therefore, muscle fatigue appears to be a unique and characteristic feature of PPS.

General and muscular fatigue in PPS have been attributed to a number of possible central and peripheral causes [43]. Proposed etiologies of central fatigue include chronic pain, respiratory dysfunction, 'type A' behavior, sleep disorders, dysfunction of the reticular activating system, and reduced dopamine secretion [44-48]. Possible causes of peripheral fatigue that involve the motor unit include metabolic exhaustion of massively enlarged post-polio motor units, neuromuscular junction transmission defects, overuse myopathy, and fiber type disproportion [4,18,49-51].

Because of similar clinical and electrophysiological features of PPS with myasthenia gravis (a known disorder of the neuromuscular junction), we have hypothesized that muscle fatigue in PPS can be attributed to neuromuscular junction transmission defects. Muscle fatigue observed in PPS is reminiscent of that in myasthenia gravis. In addition, both disorders have evidence for neuromuscular junction defects on SFEMG studies as well as on repetitive stimulation studies [3,8,38,52-54].

If terminal axonal degeneration is the cause of new weakness in PPS, it is likely that there is a period of terminal axonal dysfunction that may preceed degeneration by months to years. This period of terminal axonal dysfunction may be amenable to potential therapies that would not be useful once degeneration and denervation has occurred. Terminal axonal dysfunction may manifest itself as ineffective acetylcholine release at the nerve terminal. Terminal nerve fibers release acetylcholine into the neuromuscular junction, which then binds to acetylcholine receptors on muscle cells. This can then produce a muscle contraction. Normally, acetylcholine is rapidly broken down in the neuromuscular junction by the enzyme acetylcholinesterase. Many investigators have reported evidence for neuromuscular junction transmission defects in patients with past paralytic polio. These have included increased jitter on SFEMG, a decrement on repetitive stimulation, and an increased sensitivity to nondepolarizing muscle relaxants [3,8,38,52,56].

Investigators who have found increased jitter on SFEMG have intrepreted this finding as evidence for ongoing denervation and reinnervation in post-polio motor units as well as defective neuromuscular juction transmission. This notion was supported by findings in a recent stimulation SFEMG study which evaluated jitter at varying stimulation frequencies [57]. In a large proportion of PPS patients, jitter was significantly higher at high stimulation frequencies than at low stimulation frequencies. The patients who displayed this phenomenon were a significantly longer time since acute polio, indicating that this may be

an acquired defect following paralytic polio. In contrast, this phenomenon was a rare finding in normal controls. In addition, neuromuscular junction defects in PPS can be ameliorated with the anticholinesterase edrophonium *[51]*, providing further evidence for defective acetylcholine release as a cause for neuromuscular junction transmission defects in PPS.

Repetitive stimulation studies have also provided evidence for neuromuscular junction defects in patients with previous polio. Hodes *[52]* found a decrement of the compound muscle action potential amplitude on repetitive stimulation in patients with previous paralytic polio. He also reported an amelioration in this abnormality with anticholinesterase agents. More recent studies have shown that the decrement of the compound muscle action potential amplitude is apparent at high stimulation frequencies, but not low stimulation frequencies in patients with PPS *[58]*. This finding is consistent with previous SFEMG studies, and also suggests that acetylcholine release may be a limiting factor.

Post-polio patients are also known to have an increased sensitivity to non-depolarizing relaxants such as D-tubocurarine, pancuronium, and gallamine *[56]*. This suggests that acetylcholine release may be suboptimal in motor units following paralytic polio.

Muscle biopsy studies provide further evidence for neuromuscular junction transmission defects in post-polio muscles. Electron microscopy studies of post-polio neuromuscular junctions show dilated or bizarre terminal axons with reduced acetylcholine vesicles *[59]*. In addition, muscle of patients with past polio has been studied histochemically with neural-cell adhesion molecule (N-CAM). In normal adult muscle, N-CAM is found only at end plates, satellite cells, and intramuscular nerves *[60]*. Surface and intracellular N-CAM is known to accumulate in experimental denervation, paralysis, or fiber regeneration *[55,61]*. N-CAM immunoreactivity occurs within two days of transection, which is long before conventional muscle biopsy criteria of denervation. N-CAM then disappears on reinnervation or complete regeneration *[55,61]*. In addition, NCAM immunoreactivity on myofibers has been found to be absent in normal muscle, but present in patients with ongoing denervation or myopathies with prominent fiber degeneration and regeneration *[55]*. In patients with past paralytic polio (both stable and those with new weakness), N-CAM expression in non-atrophic muscle fibers can be 10% or more *[38]*. Because less than 1% of muscle fibers in muscle of patients with past paralytic polio are permanently denervated *[38]*, many post-polio muscle fibers may have borderline transmission of nerve impulses. Thus, N-CAM studies in post-polio muscle are consistent with significant and widespread neuromuscular junction transmission defects.

4. Contributing factors to post-poliomyelitis syndrome

Contributing factors to the development of PPS can be the normal ageing process, overuse, and disuse. The normal ageing process is known to involve a gradual dropout of motor neurons, and a decline in growth hormone and consequently IGF-1. Normal loss of motor neurons becomes prominent after age 60, and the superimposition of this process on the already limited number of motor neurons present after paralytic polio may contribute to the development of PPS *[4,9-11]*. Plasma IGF-1 has been reported to be low in patients with prior paralytic polio (including those with PPS) as compared with healthy controls *[15,16]*, although another study did not report this finding *[62]*. Despite these contradictory findings, the normal decline of growth hormone and IGF-1 could contribute to PPS. Growth hormone stimulates IGF-1 production. Both growth hormone and IGF-1 support regeneration of peripheral nerves after nerve injury, including sprouting, and muscle fiber hypertrophy *[63-68]*. In addition, in one analytic epidemiologic study a greater age at presentation to clinic was a risk factor for PPS *[69]*, whereas another study *[70]* did not confirm this finding.

Overuse is also thought to be a contributing factor to PPS. Knowlton and Bennett *[17,71]* reported several

cases of individuals 2-23 years following paralytic polio, and concluded that overuse produced increased weakness. Perry and co-workers *[18]* performed dynamic EMG studies during gait in 34 PPS patients, and found evidence of overuse primarily in the biceps femoris and quadriceps muscles. The investigators concluded from these and other studies *[72]* that overuse was the cause of PPS. In addition, increased creatinine kinase (CK) levels have been found in symptomatic patients after polio, but not in equally weak asymptomatic patients after polio *[70]*. CK levels were found to be significantly correlated with distance of ambulation in postpolio patients, suggesting that exercise is the cause of elevated CK in this population *[73]*. Since elevated CK levels can be a marker for muscle injury, the increased CK levels may indicate muscle injury or overuse in post-polio patients. In our case-control study, we found that a greater length of time after paralytic polio was a risk factor for PPS, and that muscle pain (especially that associated with exercise), joint pain, and a recent weight gain were associated with PPS *[69]*. All of these factors can be markers of overuse, providing further evidence for this theory.

Muscle disuse can also be a contributing factor to the onset of PPS. Disuse is well known to produce muscle weakness and deconditioning in normal individuals *[74]*, and most likely produces similar changes in patients with past paralytic polio *[19]*. Patients with past polio have been noted to have short-term increased weakness after a period of decreased activity secondary to illness or injury *[75]*. In our clinical experience, we have noted that periods of decreased activity may precipitate the onset of increased weakness.

5. Diagnosis of post-polio syndrome

The diagnosis of PPS is one of exclusion, and is clinically based. There is no specific diagnostic test which can distinguish symptomatic from asymptomatic survivors of past paralytic polio *[38]*. Conventional EMG, SFEMG, muscle biopsy, and N-CAM immunohistochemical studies in patients with PPS and in asymptomatic polio survivors are consistent with ongoing denervation in both groups of patients *[38]*. In addition, abnormalities indicating active denervation were found with similar frequency in both patient groups.

There are no well established diagnostic criteria for PPS. Mulder and coworkers *[76]* first proposed criteria for the onset of new weakness many years after acute paralytic polio: (1) a credible history of acute paralytic polio, (2) partial recovery of function, (3) a period of stability of at least 10 years' duration, and (4) the later development of progressive new weakness. They also suggested that there should be no other cause of the new weakness. In more recent years, Halstead *[47]*, has proposed more complete criteria for PPS. They include: (1) previous acute paralytic polio which is confirmed by history, physical examination, and EMG studies, (2) a period of recovery followed by a period of neurological and functional stability of at least 20 years' duration before the onset of new difficulties, (3) the gradual or abrupt onset of new neurogenic weakness which may or may not be accompanied by other difficulties such as excessive fatigue, muscle pain, joint pain, decreased endurance, decreased function, and atrophy, and (4) the exclusion of medical, orthopedic, or neurologic disorders which could be producing the new problems. According to this definition, new weakness should not be due to disuse although this may be difficult to ascertain. In our opinion, a more practical definition of PPS would include the above criteria with the exception of EMG studies which should be reserved for those with unclear evidence for past paralytic polio based on history or physical examination, and those who may have certain superimposed neurologic conditions (such as compressive neuropathies, or peripheral neuropathies).

6. Differential diagnosis of post-poliomyelitis syndrome

In a patient with past paralytic polio presenting with new symptoms, the diffential diagnosis will be

dependent upon the specific symptoms of the patient. It is also important to note that many patients with past paralytic polio have developed a distrust or dislike of the medical profession (perhaps due to many months of hospitalization at a young age), and may come to clinic without seeing a physician for decades. In this situation, it is important to develop a trustful relationship with the patient and to consider other disorders which could be producing any new symptoms, and which may have nothing to do with previous paralytic polio. For example, hypothyroidism and rheumatoid arthritis may produce pain, weakness, and fatigue. In our experience, undiagnosed or undertreated hypothyroidism occurs fairly frequently in patients presenting with new symptoms to a post-polio clinic, and adequate treatment results in complete or partial resolution of 'PPS.'

General fatigue is a very common symptom in the general population, and may be due to a variety of causes. Some of these causes can include respiratory dysfunction, sleep apnea, depression, sleep abnormalities, chronic pain, and a variety of medical disorders including hematologic abnormalities (e.g. anemia), endocrinological abnormalities (e.g. hypothyroidism), cardiac dysfunction, cancer, chronic systemic infections, and rheumatological disorders.

Pain in patients with past paralytic polio can be due to a variety of causes. It can be caused by muscular abnormalities, joint and soft tissues abnormalities, and other superimposed neurological abnormalities. Possible causes for muscular pain include a 'post-polio muscular pain' *[19]*, muscular overuse, muscular cramps, fasciculations, and fibromyalgia *[77]*. We have found that fibromyalgia occurs frequently in a post-polio clinic. Wolfe et al. showed that 10.5% of patients met the criteria for fibromyalgia *[78]*, whereas another 10.5% had a fibromyalgia-like syndrome with 5-10 tender points on examination. Patients with past polio who had fibromyalgia responded to specific treatment for this condition *[77]*. Treatments included low-dose, night-time amitriptyline, night-time cyclobenzaprine, fluoxetine, naproxen, and aerobic exercise *[77]*. Some of the symptoms of fibromyalgia (especially pain and fatigue) were very similar to those of PPS, however the two disorders also occurred concurrently *[77]*. Joint and soft tissue abnormalities which may produce pain include osteoarthritis, tendonitis, bursitis, degenerative disc disease, scoliosis, ligamentous strain, joint deformities, and failing joint fusions. These conditions in many cases most likely result from chronic overuse or abnormal use of joints and extremities due to muscle weakness as a result of past paralytic polio and PPS. Some superimposed neurological abnomalities which can produce pain include peripheral neuropathies, radiculopathies, and spinal stenosis.

New weakness can be due to other superimposed neurological disorders, however a variety of medical problems can also produce the symptom of new weakness. Some neurologic diseases to be considered when evaluating a patient with past paralytic polio and complaints of new weakness are listed in Table 1. These include disorders which are relatively common in the adult population such as spinal stenosis, radiculopathy, and cervical spondylosis. Other motor neuron diseases such as amyotrophic lateral sclerosis can also occur, however the frequency of this disease is not increased in those who have recovered from paralytic polio.

Table 1
Neurological disorders to exclude in diagnosing PPS[a]

Adult spinal musuclar 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
[a]These diseases may also occur concurrently with PPS. This table is reprinted with permission from Milestone Medical Communications, a Division of Ruder-Finn, from a disease management monograph entitled 'Current Trends in PostPoliomyelitis Syndrome' (1996).

7. Conclusion

In conclusion, it may be useful to consider PPS as being caused by two abnormalities in the motor unit. The first is a progressive lesion which is degeneration of terminal axons which results in permanent slowly progressive new weakness. The second is a fluctuating lesion most likely secondary to defective synthesis, storage, and release of acetylcholine, which results in neuromuscular junction transmission defects and in the symptoms of muscle fatiguability and secondary generalized fatigue. Other factors which may contribute to the development of PPS are ageing, overuse, and disuse. The diagnosis of PPS involves the exclusion of other conditions which could produce similar symptoms in a patient who presents with symptoms and signs typical for PPS.

Acknowledgements

This work was supported in part by the Fonds de la recherche en santé dy Québec, and the Association Polio Québec.

References

1. 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.
2. 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.
3. 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. [PubMed Abstract]
4. Jubelt B, Cashman NR. Neurological manifestations of the post-polio syndrome. CRC Crit Rev Neurobiol 1987;3:199-220. [PubMed Abstract]
5. 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. [PubMed Abstract]
6. Speier JL, Owen RR, Knapp M, Canine JK. Occurrence of post-polio sequelae in an epidemic population. In: Halstead LS, Wiechers DO, eds. Clinical and Research Aspects of the Late Effects of Poliomyelitis. White Plains, NY: March of Dimes Birth Defects Foundation 1987;39-48. [PubMed Abstract]
7. Munsat TL, ed. Post-Polio Syndrome. Boston, MA: Butterworth-Heinemann 1991.
8. Wiechers DO, Hubbell SL. Late changes in the motor unit after acute poliomyelitis. Muscle Nerve 1981;4:524-528. [PubMed Abstract]
9. McComas AJ, Upton ARM, Sica REP. Motoneurone disease and ageing. Lancet 1973;2:1477-1480. [PubMed Abstract]
10. Stalberg E, Thiele B. Motor unit fibre density in the extensor digitorum communis muscle. J Neurol Neurosurg Psych 1975;38:874-880. [PubMed Abstract]
11. Tomlinson BE, Irving D. The number of limb motor neurons in the human lumbosacral cord throughout life. J Neurol Sci 1977;34:213-219. [PubMed Abstract]
12. 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. [PubMed Abstract]
13. Florini JR, Print 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. [PubMed Abstract]
14. Vermeulen A. Nyctohemeral growth hormone profiles in young and aged men: correlation with somatomedin-C levels. J Clin Endocrinol Metab 1987;64:884-888. [PubMed Abstract]
15. Shetty KR, Mattson DE, Rudman IW, Rudman D. Hyposomatomedinemia in men with post-poliomyelitis syndrome. J Am Geriatr Soc 1991;185:185-191. [PubMed Abstract]
16. 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. [PubMed Abstract]
17. Bennett RL, Knowlton GC. Overwork weakness in partially denervated skeletal muscle. Clin Orthop 1958;12:22-29.
18. Perry J, Barnes G, Gronley JK. The post-polio syndrome: an overuse phenomenon. Clin Orth Rel Res 1988;233:145-162. **[Lincolnshire Library Full Text]**
19. Gawne AC, Halstead LS. Post-polio syndrome: pathophysiology and clinical management. Crit Rev Phys Rehabil Med 1995;7:147-188.
20. Salazar-Groesoe EF, Grimaldi LM, Roos RP, Variakojis R, Jubelt B, Cashman NR. Isoelectric focusing studies of serum and cerebrospinal fluid in patients with antecedent poliomyelitis. Ann Neurol 1989;26:709-713. [PubMed Abstract]
21. Sharief MK, Hentages R, Ciaidi M. Intrathecal immune response in patients with the post-polio syndrome. N Engl J Med 1991;325:749-755. [PubMed Abstract]
22. Melchers W, de Visser M, Jongen F, van Loon A, Nebbeiing R, Oostvogel P, Willemse D, Galama J. The post-polio syndrome: no evidence for poliovirus perisistence. Ann Neurol 1992;32:728-732. [PubMed Abstract]
23. Salazar-Groesoe EF, Roos RP, Jubelt B, Cashman NR. Immune responses in the post-polio syndrome. Letter to the editor. N Engl J Med 1992;326:641. [PubMed Abstract]
24. Jubelt B, Salazar-Groesoe EF, Roos RP, Cashman NR. Antibody titer to the poliovirus in blood and cerebrospinal fluid of patients with post-polio syndrome. Ann NY Acad Sci 1995;753:201-207. [PubMed Abstract]
25. Leon-Monzon ME, Dalakas M. Detection of poliovirus antibodies and poliovirus genome in patients with the post-polio syndrome. Ann NY Acad Sci 1995;753:208-218. [PubMed Abstract]
26. Leparc I, Kopecka H, Fuchs F, Janatova I, Aymard M, Julien J. Search for poliovirus in specimens from patients with the post-polio syndrome. Ann NY Acad Sci 1995;753:233-244. [PubMed

Abstract]
27. Muir P, Nicholson F, Sharief MK, Thompson EJ, Cairns NJ, Lantos P, Spencer GT, Kaminski HJ, Banatvala JE. Evidence for persistent enterovirus infection of the central nervous system in patients with previous paralytic poliomyelitis. Ann NY Acad Sci 1995;753:219-232. [PubMed Abstract]
28. Pereshkpour GH, Dalakas MC. Long-term changes in the spinal cords of patients with old poliomyelitis: signs of continuous disease activity. Arch Neurol 1988;45:505-508. [PubMed Abstract]
29. Ginsberg AH, Gale MJ Jr, Rose LM, Clark EA. T-cell alterations in late poliomyelitis. Arch Neurol 1989;46:497-501. [PubMed Abstract]
30. Dalakas MC. Pathogenetic mechanisms of post-polio syndrome: morphological, electrophysiological, virological, and immunological correlations. Ann NY Acad Sci 1995;753:167-185. [PubMed Abstract]
31. Miller DC. Post-polio syndrome spinal cord pathology: case report with immunopathology. Ann NY Acad Sci 1995;753:186-193. [PubMed Abstract]
32. Price RW, Plum F. Poliomyelitis. In: Vinken DJ, Bruyn GW, eds. Handbook of Clinical Neurology (vol. 34). Amsterdam: North Holland Biomedical Press Amsterdam: 1978;93-132.
33. Adams RD, Victor M. Principles of Neurology. New York: McGraw-Hill Book Company 1993;641-644.
34. Bodian D. Poliomyelitis: pathological anatomy. In: Poliomyelitis (papers and discussions presented at the First International Poliomyelitis Congress). Philadelphia: Lippincott 1948;62-84,100-101.
35. 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.
36. 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.
37. Wiechers DO. New concepts of the reinnervated motor unit revealed by vaccine-associated poliomyelitis. Muscle Nerve 1988;11:356-364. [PubMed Abstract]
38. 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. [PubMed Abstract]
39. Lange DJ, Smith T, Lovelace RE. Post-polio muscular atrophy: diagnostic utility of macroelectromyography. Arch Neurol 1989;46:502-506. [PubMed Abstract]
40. 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. [PubMed Abstract]
41. 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. [PubMed Abstract]
42. Berrly MH, Stauser WW, Hall KM. Fatigue in post-polio syndrome. Arch Phys Med Rehabil 1991;72:115-118.
43. 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. [PubMed Abstract]
44. 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. **[Lincolnshire Library Full Text]**
45. 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. [PubMed Abstract]
46. 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. [PubMed Abstract]
47. Halstead LS. Post-polio syndrome: definition of an elusive concept. In: Munsat TL, ed. Post-Polio Syndrome, Boston, MA: Butterworth-Heinemann, 1991;23-28.
48. Bruno RL, Zimmerman JR, Creange SJ, Lewis T, Molzen T, Frick NM. Bromocriptine in the treatment of post-polio fatigue: a pilot study with implications for the pathophysiology of fatigue. Am J Med Rehabil 1996;75:340-347. **[Lincolnshire Library Full Text]**
49. 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. [PubMed Abstract]
50. Munsat TL, Andres P, Thibodeau L. Preliminary observations on long-term muscle force changes in the postpolio 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. [PubMed Abstract]
51. Trojan DA, Gendron D, Cashman NR. Anticholinesterase-responsive neuromuscular junction transmission defects in post-poliomyelitis fatigue. J Neurol Sci 1993;114:170-177. **[Lincolnshire Library Full Text]**
52. Hodes R. Electromyographic study of effects of neuromuscular transmission in human poliomyelitis. Arch Neurol Psych 1948;60:457-473.
53. Stalberg E, Schwartz MS, Trontelj JV. Single fiber electromyography in various processes affecting the anterior horn cell. J Neurol Sci 1975;24:403-415. [PubMed Abstract]
54. Engel AG. Acquired autoimmune myasthenia gravis. In: Engel AG, Banker BQ, eds. Myology. New York: McGraw Hill 1986;1925-1954.
55. Cashman NR, Covault J, Wollmann RL, Sanes J. Neural cell adhesion molecule in normal, denervated, and myopathic human muscle. Ann Neurol 1987;21:481-489. [PubMed Abstract]
56. Gyermek L. Increased potency of non-depolarizing relaxants after poliomyelitis. J Clin Pharm 1990;30:170-173. [PubMed Abstract]
57. 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. **[Lincolnshire Library Full Text]**
58. Trojan DA, Gendron D, Cashman NR. Repetitive stimulation studies in post-poliomyelitis syndrome. Arch Phys Med Rehabil 1996;77;925. (Abstract)
59. Maselli RA, Wollmann R, Koos R. Function and ultrastructure of the neuromuscular junction in post-polio syndrome. Ann NY Acad Sci 1995:753:129-137. [PubMed Abstract]
60. Covault J, Sanes JR. Distribution of N-CAM in synaptic and extrasynaptic portions of developing and adult skeletal muscle. J Cell Biol 1986;102:716-730. [PubMed Abstract]
61. Covault J, Sanes JR. Neural cell adhesion molecule (N-CAM) accumulates in denen/ated and paralyzed adult skeletal muscles. Proc Natl Acad Sci USA 1985;82:4544-4548. [PubMed Abstract]
62. Sunnerhagen KS, Bengtsson GA, Lundberg PA, Landin K, Lindstedt Goran, Grimby G. Normal concentrations of serum insulin-like growth factor-1 in late polio. Arch Phys Med Rehabil 1995;76:732-735. [PubMed Abstract]
63. Froesch ER, Schmid C, Schwander J, Zapf J. Action of insulin-like growth factors. Ann Rev Physiol 1985;47:443-467. [PubMed Abstract]
64. 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 Endocrin Metab 1986;62:753-759.
65. Roeder RA, Hossner KL, Sasser RG, Gunn JM. Regulation of protein turnover by recombinant human insulin-like growth factor-1 in L6 myotube cultures. Horm Metab Res 1988;20:698-700. [PubMed Abstract]
66. Kanje M, Skottner A, Lundborg G. Effects of growth hormone treatment on the regeration of rat sciatic nerve. Brain Res 1988;475:254-258. [PubMed Abstract]
67. Kanje M, Skottner Sjoberg L, Lundborg G. Insulin-like growth factor 1 (IGF-1) stimulates regeneration of sciatic nerve. Brain Res 1989;486:396-398. [PubMed Abstract]
68. 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. [PubMed Abstract]
69. Trojan DA, Cashman NR, Shapiro S, Tansey CM, Esdaile JM. Predictive factors for post-poliomyelitis syndrome. Arch Phys Med Rehabil 1994;75:770-777. **[Lincolnshire Library Full Text]**
70. 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. [PubMed Abstract]
71. Knowlton, GC, Bennet, RL. Overwork. Arch Phys Med Rehabil 1957;38:18-20.
72. Perry J, Fontaine JD, Mulroy S. Findings in postpoliomyelitis syndrome. J Bone Joint Surg 1995;77A: 1148-1153. **[Lincolnshire Library Full Text]**
73. Waring WP, McLaurin TM. Correlation of creatinine kinase and gait measurement in the post-polio population: a corrected version. Arch Phys Med Rehabil 1992;73:447-450. [PubMed Abstract]
74. Muller EA. Influence of training and of inactivity on muscle strength. Arch Phys Med Rehabil 1970;51:449-462. [PubMed Abstract]
75. Agre JC, Rodriquez AA, Tafel JA. Late effects of polio: critical review of the literature on neuromuscular function. Arch Phys Med Rehabil 1991;72:923-931. [PubMed Abstract].
76. Mulder DW, Rosenbaum RA, Layton DD. Late progression of poliomyelitis or forme fruste amyotrophic lateral sclerosis? Mayo Clin Proc 47;1972:756-761. [PubMed Abstract]
77. Trojan DA, Cashman NR. Fibromyalgia is common in a post-poliomyelitis clinic. Arch Neurol 1995;52:620-624. **[Lincolnshire Library Full Text]**
78. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, Fam AG, Farber SJ, Fiechtner JJ, Franklin CM, Gatter RA, Hamaty D, Lessard J, Lichtbroun AS, Masi AT, McCain GA, Reynolds WJ, Romano TJ, Russell IJ, Sheon RP. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Arthritis Rheum 1990;33:160-172. [PubMed Abstract]

This article is part of a collection of post-polio related articles that appeared together in one issue of NeuroRehabilitation. A number of those articles are available in the Lincolnshire Post-Polio Library. See NeuroRehabilitation 8 (1977)

The Lincolnshire Post-Polio Network
Registered Charity No. 1064177
An Information Service for Polio Survivors and Medical Professionals

All enquiries, book requests, medical article requests, membership fees, items for newsletters and donations to
The Secretary, Lincolnshire Post-Polio Network
PO Box 954, Lincoln, Lincolnshire, LN5 5ER United Kingdom
Telephone: +44 (0)1522 888601
Facsimile: +44 (0)870 1600840
Email: info@lincolnshirepostpolio.org.uk
Web Site: www.lincolnshirepostpolio.org.uk

The Lincolnshire Post-Polio Network takes great care in the transcription of all information that appears at this site. However, we do not accept liability for any damage resulting directly or otherwise from any errors introduced in the transcription. Neither do we accept liability for any damage resulting directly or otherwise from the information available at this site. The opinions expressed in the documents available at this site are those of the individual authors and do not necessarily constitute endorsement or approval by the Lincolnshire Post-Polio Network.

Document preparation: Chris Salter, Original Think-tank, Cornwall, United Kingdom.
Document Reference: <URL:http://www.zynet.co.uk/ott/polio/lincolnshire/library/trojan/pathophysiology.html>
Created: 16th September 1998.
Last modification: 30th January 2010.