Lack of progression of neurologic deficit in survivors of paralytic polio:

A 5-year prospective population-based study

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Article abstract—We completed a prospective, population-based cohort study of polio survivors in Olmsted County, Minnesota, between 1986 and 1993. We identified 50 individuals who had had paralytic polio between 1935 and 1960, as representative of all 300 cases of paralytic polio in the county. We completed detailed quantitative clinical and electrophysiologic studies at entry and after 5 years. These studies demonstrated stable neuromuscular function within the cohort, although 60% of the individuals were symptomatic. In two-thirds of the symptomatic patients, the causes of their symptoms were unrelated to earlier polio. For the 20% of patients who had unexplained muscle pain, perception of weakness, and fatigue, a mechanical disorder most likely underlies their symptoms.

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After the introduction of immunization programs in the mid-1950s, poliomyelitis was rapidly eradicated in developed nations. Patients with acute anterior poliomyelitis typically had an acute biphasic viral illness with fever, headache, and gastrointestinal symptoms followed several days later by the rapid development of limb and bulbar paralysis. This paralysis was caused by invasion of motor neurons by the neurotrophic polio virus, followed by neuronal death. Progression of paralysis usually stopped after 5 to 7 days. There was then a period of stability followed by some degree of gradual recovery of function. This recovery was caused by sprouting and reinnervation of muscle by surviving motor neurons, and it progressed over months to years and was followed by prolonged stability of neuromuscular function. During the past 10 years, late progression of symptoms and neuromuscular deficit has been reported in persons who had paralytic polio. This has been reported for many years[1,2] as a rare, late sequela of polio. In affected patients, progressive atrophy and weakness developed after at least 10 to 15 years of stable function. This change was speculated to result from age-related attrition of motor neurons from the motor neuron pool already depleted by the viral illness. This entity of late progressive weakness and atrophy has been named *postpolio progressive muscular atrophy*. A second type of symptom cluster in survivors of paralytic polio was described in 1987.[3] Patients were identified with symptoms of progressive muscle pain, weakness, and fatigue. This was named *postpolio syndrome*. The prevalence of these symptoms is unknown but is estimated to be approximately 70% of polio survivors.

To understand the frequency and basis of these symptoms, we used the unique resources of the Olmsted County, Minnesota, database at the Mayo Clinic. Since the early part of this century, residents of Rochester and Olmsted County, Minnesota, have received their medical care primarily at the Mayo Clinic and its affiliated hospitals. All physician contacts resulted in a diagnosis that was coded for automated retrieval. Diagnoses of Olmsted County residents receiving medical care at other institutions or practices in Olmsted and surrounding counties were also linked for retrieval within the same system. This allowed us to identify all patients within a defined community of 100,000 who had paralytic poliomyelitis between 1935 and 1960. A representative cohort from this population was identified and followed prospectively with detailed clinical and electrophysiologic studies. Each individual was studied for 5 years. The entry characteristics of this cohort were described previously.[4] We now report the results of a 5-year followup study.

Methods. *Patient population.* We previously described the demographic characteristics of the study population in detail.[4] Briefly, 608 residents with acute poliomyelitis between 1935 and 1960 were identified. Three hundred individuals met the criteria for paralytic poliomyelitis, 298 of whom were available for followup; we chose a representative cohort of 50 individuals for prospective, sequential evaluations. They were chosen because they represented the whole cohort—in terms of number of limbs involved,

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bulbar involvement, severity of involvement, likelihood of being ventilated, age at time of polio, current age, interval since polio, gender, and cerebrospinal fluid protein findings—and not because of ongoing symptoms. All patients had detailed quantitative neurologic examinations performed at the worst point of their acute illness.[4,5] Of the 50 patients, 46 completed the detailed 5-year study. Four patients declined to complete the tests but were contacted by telephone; all four reported that they were asymptomatic and did not want to participate in further detailed physiologic testing. The 5-year prospective study involved repeating all of the tests and examinations that were done at entry.[4]

Questionnaire. Each person completed a detailed questionnaire history.[5] This was modified with additional questions that concerned the status of symptoms between the first and second (5-year interval) evaluations. All questions at both entry and followup were answered in a yes/no format.[4,5] The questionnaire contained 337 items about limb and bulbar weakness, pain, fatigue, and activities of daily living. Specific examples of the format for questions have been published.[5] For data analysis, certain key items were extracted from this questionnaire to devise a progression score. For example, in response to the statement, "The arm weakness has worsened during the last 5 years," a positive answer was assigned one point. This progression score would yield a maximum of 50 points for subjects who thought they were maximally deteriorating in every aspect of their function. The score is a simple way of adding the number of symptoms from a standardized questionnaire that allows graphic representation of symptoms without implying a linear relationship between symptom score and severity of disease.

Neurologic disability score. This scored and validated[4,6] neurologic examination was performed for all patients. For this study, only muscle strength scores were used. A score of 0 represents completely normal bulbar, trunk, and limb muscle strength; a score of 216 represents complete paralysis of all muscles. The neurologists (A.J.W. and W.J.L.) completing the examinations were unaware of the symptom status of the patient and did not have the results of the first examination available when the second examination was performed 5 years later.

Electrophysiology. All patients underwent bilateral ulnar, median, and peroneal motor and ulnar, median, and sural sensory nerve conduction studies at both evaluations, performed by the same neurologist (J.R.D.). Compound muscle action potentials (CMAP) were recorded at identical locations by anatomic landmarks. Technique and reproducibility have been reported.[6] We estimated the number of motor units (MUNE) present in median innervated thenar muscles and peroneal innervated extensor digitorum brevis muscles bilaterally with a statistical modification[7] of the McComas method.[8]

Biomechanical measurement of muscle strength. Isometric strength was measured in the Mayo Biomechanics Laboratory. The method has been described in detail.[9,10] Identical techniques were used at both evaluations. Strength was evaluated bilaterally for the following joint movements: elbow flexion and extension, forearm pronation and supination, knee flexion and extension, and ankle extension and flexion. Data were normalized for each movement by decade, gender, height, weight, and side of dominance.[10]

Function and timed tests. A battery of functional tests was performed under standard conditions at both evaluations. Lower limb function was measured as the time to walk 100 feet as quickly as possible in the physical therapy gymnasium. The time to complete an upper limb dexterity function was assessed with two standardized pegboard tests—the Minnesota Rate of Manipulation test and the Crawford Small Parts Dexterity test.

Data analysis. This study generated more than 20,000 individual data points, enabling a large number of cross-correlations. Overall, parametric statistical techniques were used unless stated. Where appropriate, Student's *t*-test, analysis of variance, chi-square test, and linear regression analysis with the method of least squares were used.

Results. *Patients.* Of the original cohort of 50 subjects, 46 returned to complete the studies. Of the four who did not return, two completed the symptom questionnaire and two reported by telephone that they were doing well. No data were analyzed from the two subjects interviewed by telephone. Of the 46 subjects who returned for testing, 42 completed all studies; 4 did not complete the electrophysiologic ones.

Stability of symptoms. The symptom score was designed to elicit symptoms of muscle or joint pain, fatigue, progressive weakness, or progressive muscle atrophy. Twenty-three individuals had at least one of these complaints at the first and second evaluations, 12 had no complaints at either evaluation, 7 had complaints at the first evaluation but did not have a complaint at the second, and 6 had no complaints at the first evaluation but did have a complaint at the second. This finding suggests a relative stability of complaints ($p = 0.0055$, Fisher's exact test). When the individual types of complaints (pain, weakness, fatigue, or atrophy) were analyzed, the distribution was similar. The extent of complaints in each patient has been reported elsewhere.[11]

The symptoms of pain, weakness, fatigue, and atrophy make up the postpolio syndrome. However, those are nonspecific symptoms, especially in an aging population. At the second evaluation and in the analysis, we sought alternative explanations for the specific symptoms reported by the patients. Twenty patients had an explanation for their symptoms that was not related to failing neuromuscular function: 14 had radiologically demonstrated degenerative joint disease that accounted for their pain and 6 had one each of diabetes, fatigue due to a 30-pound weight gain, alcoholism, depression, the residual of a motorcycle accident, and acute lumbar disc herniation.

Neurologic disability score and timed tests of function. Neurologic disability scores (NDSs) remained stable. Regression analysis showed that both the mean of the population and the individuals within that population did not change. When NDSs after 5 years were plotted against initial NDSs, the slope of the line was 1 and the correlation coefficient was highly significant ($r^2 = 0.95$). The intercept of the regression line was −2.45, indicating improvement of the population. The mean NDS improved slightly but significantly from 20.3 ± 3.6 at the first evaluation to 17.1 ± 3.7 ($p = 0.0036$, paired Student's *t*-test) at the second evaluation. In parallel, the time to walk 100 feet had im-

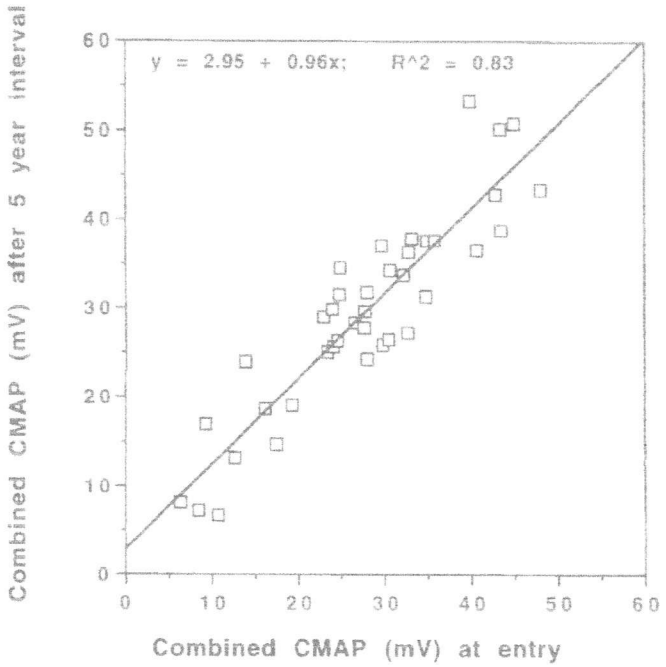

Figure 1. Regression of summated compound muscle action potentials (CMAP) amplitudes (right and left thenar plus right and left extensor digitorum brevis muscles) at the second examination (5-year interval) compared with the summated CMAP amplitude at the first evaluation. The amplitudes are stable (slope = 0.96) and reproducible within individual subjects ($r^2 = 0.83$).

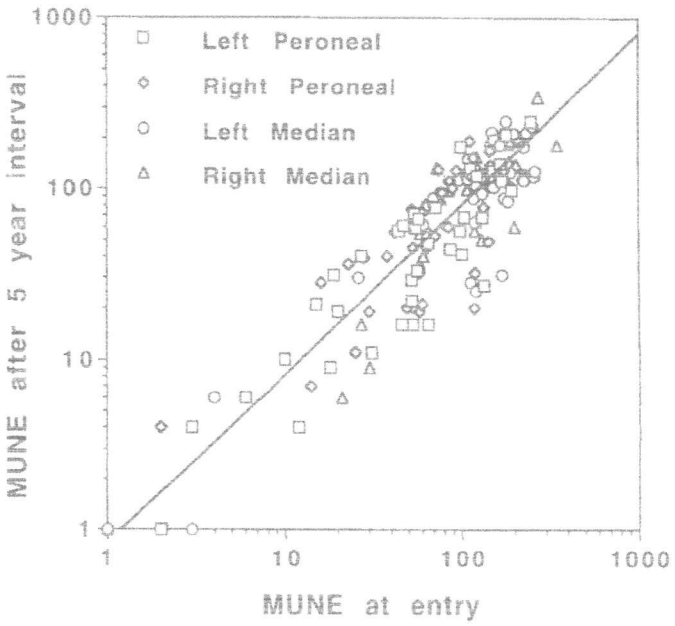

Figure 2. Regression of motor unit number estimates (MUNE) at the second examination (five-year interval) compared with MUNE at the first evaluation. The peroneal nerve was stimulated at the fibular head recording over the extensor digitorum brevis muscle. The median nerve was stimulated at the elbow with recording over the abductor pollicis brevis muscle.

proved slightly but significantly (from 27.6 ± 1.1 to 23.6 ± 1.3 seconds; $p < 0.0001$), whereas results of upper limb function tests had not changed (Minnesota Rate of Manipulation, 39.2 ± 5.1 sec to 41.0 ± 5.7 sec, $p = 0.4$; Crawford Small Parts Dexterity test, 52.1 ± 5.0 sec to 48.3 ± 5.1 sec, $p = 0.23$). Data sets have been filed with the National Auxiliary Publication Service (NAPS).

Electrophysiology. We have demonstrated[9] that the summation of CMAP is a clinically useful way of generating a single estimate of muscle function for an individual. Regression analysis of these data (figure 1) showed population and individual stability when the two evaluations were compared. As with the previous data set, there was a slight but significant (two-tailed test, $p = 0.0195$) improvement in mean CMAP from 27.7 ± 1.5 mV to 29.3 ± 1.8 mV between the two evaluations. MUNE was also stable. Electrophysiologic data are available through NAPS.

Secondary analysis of data. Because poliomyelitis and the residua are multifocal, we were concerned that significant changes in paretic limbs might be masked by stability in uninvolved limbs. To make comparisons, we considered five separate parts for each subject: bulbar musculature, right and left upper limbs, and right and left lower limbs. We then determined whether a part had been involved by the original disease process on the basis of the original record available at the height of the acute paralytic illness. The neurologic record[10-13] was instituted in 1917 at Mayo Clinic; all patients in this study had detailed, complete records from the time of their acute illness. This analysis yielded 115 normal or unaffected limbs and 135 paretic limbs. We then compared each of our measurements (NDS, CMAP, and MUNE isometric and isometric strengths) for a limb between the first and second evaluations. For each measurement, we considered only the measurements for the muscles in that limb. These comparisons showed no difference between the control and paretic limbs, except for a small but significant improvement in function of the paretic limbs (mean change in NDS for unaffected limbs, 0.15 ± 1.0 versus 0.76 ± 2.9 for paretic limbs during the 5-year interval; $p = 0.046$ in the direction of improvement).

The other approach to secondary analysis was to compare subjects who thought they were having new difficulties with those who were not. This showed no significant difference between groups (data tables filed with NAPS).

Finally, we considered the 10 patients who complained of pain, weakness, and fatigue but had no other explanation for these symptoms. All these patients had the symptoms at the second evaluation; thus, the symptoms were stable and had been present at both evaluations or had appeared since the first evaluation. The NDS had decreased in this group from 21.2 ± 6.0 to 14.9 ± 5.0 (SEM). In the control group, the NDS decreased from 19.7 ± 4.3 to 17.7 ± 4.6 (SEM). This group had either no symptoms or symptoms with an adequate explanation (as described above). The improvement in NDS was significantly greater ($p = 0.01$) for the symptomatic group than for the controls. We made a similar comparison for the summated CMAP. This improved by 1.3 ± 0.9 mV (SEM) for the control compared with 3.3 ± 1.5 mV for the symptomatic group. This difference was not significant ($p = 0.26$). There was no significant difference for the change in MUNE between the groups. Additional analyses included regression of ΔCMAP, ΔNDS, and ΔMUNE against age at onset of dis-

case, interval since acute disease, age at second evaluation, maximal NDS during acute illness, and weight gain. No correlations were found.

Discussion. This prospective study demonstrated remarkable stability of neuromuscular function in a group of survivors of paralytic polio. Several attributes of neuromuscular function actually improved in the group during the 5-year observation period. The indications of better neuromuscular function were all small but statistically significant. They are reliable indicators and are different ways of measuring muscle function: The NDS is a clinical examination, walking 100 feet is a timed test of function, and CMAP is an objective electrophysiologic measure. The results raised the question of whether, even in this mature population, 35 to 50 years after the acute illness, reinnervation is still occurring. Our subjects underwent no specific therapy as a result of participation in this study.

The observation of improvement or stability raises questions about the sensitivity of the techniques used to detect change. When we designed the prospective study, we chose the primary techniques because they had been validated and shown to be sensitive to change in diabetic neuropathy, an indolently progressive neuromuscular disorder that has a time course of change similar to that of symptom reports in polio survivors. Our inability to detect deterioration was not likely due to a lack of sensitivity of the measuring instruments. The high degree of correlation between measurement at the first and second evaluations further validates the measurements. Other groups that have detected deterioration on retrospective analyses had preliminary findings that were similar to ours when they used a prospective design.[14,15]

We found that symptoms reported in polio survivors included combinations of pain, weakness, and fatigue.[16] These symptoms, which have been reported as being components of postpolio syndrome, were present in approximately 60% of our cohort. Twenty of the 30 patients with these symptoms had other causes that completely explained their symptoms. We believe this was an important observation. If a patient who had polio presents with one or more of these symptoms, postpolio syndrome should not be diagnosed automatically. If this group is representative, then in about two-thirds of symptomatic patients an alternative cause will be found, which has different therapeutic implications.

These findings raise questions about postpolio syndrome as a distinct clinical entity. Undoubtedly, patients who had polio do have these symptoms. In our group, 20% of patients had pain, perception of progressive weakness, and fatigue with no alternative explanation. However, it is equally clear that the symptoms in this group are not based on progressive neuromuscular failure. The subset of 10 patients with these symptoms had stable or improving neuromuscular function. Although the cause of these symptoms remains unknown, they are similar to symptoms present in patients with chronic fatigue syndrome. This disorder is often associated with depression, which was absent from our cohort, as determined from evaluations with the Minnesota Multiphasic Personality Inventory at both visits. Depression scales were normally distributed at the first[4] and second visits (data not shown).

Another neuromuscular disorder associated with muscle pain and perception of weakness and fatigue is tension myalgia, or fibromyalgia.[17] This disorder is not usually associated with depression and involves muscle pain, usually at tendon insertion, that is worsened with and may persist after use or overuse. The disorder is common in middle-aged, deconditioned persons. Because of the degree of similarity in symptoms between our subset of patients and those with fibromyalgia, we believe this is a reasonable alternative diagnosis. In neither case is there any evidence of intrinsic nerve or muscle disease. The incidence of fibromyalgia in the population is unknown, so we cannot say whether it is more common in polio survivors. The chronic use of weak muscles or muscles acting in a compensatory fashion may well predispose persons to this type of problem. If this is the cause of postpolio syndrome, it leads directly to therapeutic strategies. Patients with fibromyalgia can be effectively treated with conditioning, physical medicine approaches, and tricyclic antidepressants.[17] Because there was no evidence of progressive neuromuscular deterioration, there is no basis for the use of drugs designed to improve neuromuscular function.

The second disorder that has been associated with late-onset weakness after polio is postpolio progressive muscular atrophy. This was originally described by Mulder et al[2] as a rare, late complication of polio. We did not detect any case within our cohort. Each of the investigators has, however, seen patients with this disorder in their referred practice. This usually involves painless and slowly progressive weakness and atrophy in muscles that were often severely affected by the original disease.[11] We would concur with Mulder et al that this is a rare disorder of sufficiently low incidence that it was not detected in a cohort of 50 persons at risk.

The cohort was representative of polio survivors in the United States. The population of Olmsted County from 1935 to 1960 was of predominantly northern European descent (German, Irish, and Scandinavian). It does not represent populations of different race or ethnicity. The type of polio epidemic that occurred in the upper Midwest was similar to those occurring throughout the United States and Europe. The cohort was also representative in terms of severity of original disease and sites of involvement.[4] For all these reasons, we believe that our findings can be extrapolated to the whole population of polio survivors in the United States. Overall, these findings are reassuring. This group has no evidence of progressive neuromuscular failure, and rational

therapeutic approaches may produce substantial benefits.

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Note. Readers can obtain five pages of supplementary material from the National Auxiliary Publications Service, c/o Microfiche Publications, PO Box 3513, Grand Central Station, New York, NY 10163-3513. Request document no. 05224. Remit with your order (not under separate cover), in US funds only, $7.75 for photocopies or $4.00 for microfiche. Outside the United States and Canada, add postage of $4.50 for the first 20 pages and $1.00 for each 10 pages of material thereafter, or $1.75 for the first microfiche and $.50 for each fiche thereafter. *There is a $15.00 invoicing charge on all orders filled before payment.*

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