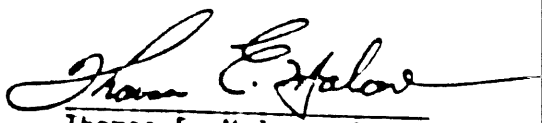
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Institutes of Health

National Institute of Neurological and Communicative Disorders and Stroke

Report on Latent Effects of Polio



Thomas E. Malone, Ph.D.
Deputy Director, NIH

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Executive Summary

In Report No. 99-151, the Senate Committee on Appropriations requested that the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) prepare and submit a report regarding the research efforts which are being conducted concerning the latent effects of polio. The following report is submitted in response to that request.

Some persons with a history of acute paralytic poliomyelitis not only experience residual muscle weakness from the initial illness, but they also develop new neuromuscular symptoms later in life. This later condition is termed late postpoliomyelitis muscular atrophy (late PPMA), or more commonly, post-polio syndrome. The symptoms in late PPMA may vary in form and severity from simple decline of musculoskeletal function to the development of new progressive muscle weakness and symptoms which may appear to be similar to typical cases of amyotrophic lateral sclerosis (ALS). The cause and frequency of these symptoms are unknown. Some of the proposed explanations include the reactivation of polio virus or a normal aging process in previously affected muscle groups which are innervated by an already depleted number of motor neurons. Research observations of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) suggest that the new progressive muscle weakness that occurs in some of these persons is definitely not ALS, but may involve a defect in the immune system. Whether a persistent viral infection is involved remains to be determined.

Report on Latent Effects of Polio

INTRODUCTION

In its report on the Fiscal Year 1986 budget for the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) of the Department of Health and Human Services, the Senate Committee on Appropriations stated:

> "It has come to the attention of the Committee that many of the 300,000 Americans stricken by polio in the 1950's are once again suffering from muscle weakness and excruciating pain. Therefore, the Committee directs NINCDS, in consultation with CDC, to inform the Committee prior to the fiscal year 1987 budget hearings regarding the research efforts which are being conducted in this area." (Senate Report No. 99-151, page 76)

The following report has been prepared by the NINCDS of the National Institutes of Health, Department of Health and Human Services in response to this request.

BACKGROUND

Polio was a contagious and terrifying disease in the United States until 1955 when Dr. Jonas Salk's vaccines were first widely used. There are now approximately 300,000 U.S. survivors of the polio epidemics of the 1940's and 1950's. While most persons who have had polio stabilize and never have any additional muscle-related problems, several thousand recovered polio victims not only experience residual muscle weakness from the initial illness, but also develop new neuromuscular symptoms later in life. Some have been affected recently with new symptoms of muscle and joint pain and weakness that, in a few cases, have been more serious than the original disease. Estimates based upon several preliminary surveys of polio survivors indicate that between 60,000 and 75,000, or 20 to 25 percent of the survivors, may eventually suffer these late effects. One group of these persons is afflicted with a condition which has been termed late postpoliomyelitis muscular atrophy (late PPMA) or, more commonly, post-polio syndrome.

The symptoms these persons with late PPMA experience may vary in form and severity from simple decline of musculoskeletal function to the development of new progressive muscle weakness and symptoms which may appear to be similar to typical cases of amyotrophic lateral sclerosis (ALS). The cause and frequency of these symptoms are unknown. Some of the proposed explanations include the reactivation of polio virus or a normal aging process in previously affected muscle groups which are innervated by an already depleted number of motor neurons. One theory proposes that the weakness and pain stem from overloaded nerve cells of the spinal cord that control muscle movement (anterior horn cells). Many of these cells are destroyed during the original invasion of the polio virus. If some of the cells are damaged, but not destroyed, they too might be expected to fail after years of compensating for lost nerve cells. Recent findings indicate that disorders of the immune system may play a role.

RECENT RESEARCH FINDINGS / ONGOING RESEARCH

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) is the focal point for research on disorders of the nervous system, including late postpoliomyelitis muscular atrophy (PPMA). Basic and clinical studies under way in NINCDS laboratories or at grantee institutions are focusing on many encouraging theories and leads.

During the last four years, a clinical research study of PPMA has been conducted in NINCDS laboratories in the Warren Grant Magnuson Clinical Center at the National Institutes of Health. Scientists are conducting a series of studies on patients with a remote history of paralytic poliomyelitis who are now experiencing new symptoms. They are attempting to define the clinical symptoms experienced by some polio survivors and are exploring possible causes of the disorder, such as a late polio virus infection, an immunologic defect, or the effects of aging on already damaged or weakened nerve cells. Specifically, these multidisciplinary studies are directed to answering the following questions:

1. What are the symptoms that some of the post-polio patients develop and do these fall into clear diagnostic groups?
2. What are the possible mechanisms or the causative agents of the new muscle weakness?
3. What is the prognosis of the post-polio new weakness?
4. How often do patients with old polio develop new symptoms?
5. Are there any effective therapies or experimental therapeutic interventions?

The approach and findings with regard to each of the above cited questions is as follows:

1) What are the symptoms that some of the post-polio patients develop and do these fall into clear diagnostic groups?

The patients selected for study fulfilled the following criteria: a) partial recovery of motor function and minimum of a 10-year period of functional stabilization after extensive rehabilitation, b) signs of some residual neurological deficit, and c) a report of experiencing new neuromuscular symptoms.

From a careful clinical and neurological examination, scientists were able to distinguish two categories of symptomatic post-polio patients. Although post-polio decline of either type is not new, the majority of cases have been recognized within the last 4 or 5 years.

One group of patients had diminished functional capacity and subsequent stabilization without development of identifiable new weakness. These patients, most of whom had been left with severe disability from the original disease, had predominantly musculoskeletal rather than neurological complaints. Their most common symptoms included joint pains, diminished stamina, frequent falls, recurrent injuries, instability of gait, and need to return to bracing or fitting of new braces. They appeared to remain relatively stable for long periods, often functioning at the lower level or

by reducing their work demands. During a three year follow-up evaluation, these patients showed no neurologic change. Research scientists feel that these symptoms likely are caused by accelerated aging, rather than a disease process.

A second group of post-polio patients presented with what has been named post-poliomyelitis muscular atrophy or PPMA. These patients experience 30 to 40 years of stability before the new symptoms begin. Groups of muscles start to ache and lose their strength. The patients frequently drop objects or find it difficult to climb stairs. The new symptoms in these patients were characterized by asymmetrical and very slowly progressive new muscle weakness, muscle wasting, muscle cramps and occasionally muscle pains. These symptoms involved muscles which were affected during the original disease and had partially or fully recovered or muscles that were clinically unaffected during the original illness. PPMA had unique clinical characteristics, distinguishing itself from other neurological illnesses, and appeared to be very slowly progressive. Unlike the initial polio attack, which could debilitate patients within days, this new muscle weakness is mild and develops more slowly. Typically, new changes are noticeable only every one to three years. None of the post-polio patients that have been examined at NIH presented with or developed amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease). Although the new post-polio muscle weakness probably results from a loss of movement-controlling neurons, the same cells affected in ALS, research indicates that the new weakness is definitely not ALS.

The researchers have, in addition, defined the objective laboratory criteria that appear to be necessary for the practicing physician to make the diagnosis of PPMA. These included a series of electromyographic studies as well as muscle biopsies from the newly affected muscles. The combination of these studies is now very helpful in confirming the diagnosis of PPMA.

2) <u>What are the possible mechanisms or the causative agents of the new muscle weakness</u>?

The cause of the suspected neuron loss, and subsequent muscle weakness, is unclear. A series of immunological, virological, electrophysiological and histological studies have been performed. The spinal fluid of patients with PPMA was studied and compared with the spinal fluid of patients without symptoms for the presence of abnormal proteins (immunoglobulins) or elevation of antibody to viruses including poliomyelitis virus. This was useful in helping determine whether there is evidence in patients with PPMA for possible reactivation of the poliomyelitis virus. These studies have thus far failed to show that PPMA is causally related to a latent infection with poliomyelitis virus. Further studies are now in progress to investigate with new technological means whether poliomyelitis virus plays a role in the development of new symptoms in these patients.

Examination of the muscle biopsies from patients with PPMA using special techniques revealed abnormalities in the newly weakened muscles which suggest that in PPMA the surviving motor nerve cells (anterior horn cells) in the spinal cord can no longer maintain the metabolic needs of their nerve terminals which serve distant muscles. These findings were reinforced with a sophisticated electromyographic analysis. Based on these findings the hypothesis now is that in PPMA not the whole nerve cell but the most distant

part of its motor axon (branch) disintegrates and cannot further maintain its service to muscle tissue. This may be due to the fact that in post-polio patients the surviving motor neurons have overcompensated for the ones lost during the previous polio illness by sprouting new branches in an attempt to control a larger area of muscle function. After a certain number of years the surviving neurons are not able to maintain fully the metabolic properties of the most distant part of the nerve axons and cannot support further sprouting. This results in new muscle deterioration and weakness.

Some evidence suggests that the new weakness may involve a defect in the immune system. The body may be reacting against its own nerve cells. A surprising finding which is now being examined is the presence of two abnormalities related to a possible immune disorder -- the presence of abnormal immunoglobulins in the spinal fluid, and the finding of inflammatory cells in the muscle biopsy. Although these suggest involvement of possible immune mechanisms, research scientists have not found any abnormalities of the immunoregulatory system in PPMA patients.

3) What is the prognosis of the new post-polio weakness?

Post-polio patients have been very frightened and uncertain about the rate of progression of their new weakness and the possibility of developing a new disability. In order to answer this question scientists have re-examined patients that they had seen at the National Institute of Neurological and Communicative Disorders and Stroke several years ago with what appeared to be PPMA. The follow-up examination was performed after an average period of 11.6 years from the time these patients were originally examined and studied neurologically. From these analyses the scientists were able to determine that the new post-polio weakness is a slowly progressive disease. The rate of progression on a year to year basis was estimated to be about 1% of his/her total neuromuscular function per year, although this may be unpredictible. The progression is, however, so minimal that objective new weakness becomes appreciable, not on a year-to-year basis, but on cumulative periods of 2-3 years. Of major interest is the fact that none of the patients during this long follow-up examination developed amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease).

Although PPMA appears not to be a life-threatening illness, it can result in new disability in patients who are already left with weakness from the original disease and have very little muscle reserve. On the other hand, patients who have been left with very minimal disability from the original disease do not appear to have a significant new disability, although the presence of some new symptoms are extremely bothersome.

4) How often do patients with old polio develop new symptoms?

Scientists are in the process of analyzing the symptoms of 2,500 military veterans afflicted with polio several years ago. Letters have been mailed to all these veterans with a questionnaire asking whether they have been experiencing new neuromuscular symptoms which caused new disability or interfered with their lifestyles. Scientists are analyzing these data hoping to be able to provide some information as to how frequent the new symptoms are, how many years after the acute polio they seem to appear, and what other factors may be directly or indirectly implicated in their development. The researchers are also planning to examine a select group of those patients and

confirm the presence of new disease with a series of neurological, electrophysiological, virological, and immunological studies as described above.

5) Are there any effective therapies or experimental therapeutic interventions?

At the moment there is no therapy for the disease. It is possible, however, to categorize these patients and provide them with explanations concerning the nature of the disease. In addition, it is possible to provide reassurance that PPMA progresses very slowly and that it is not a recurrent polio.

For symptomatic relief, rehabilitation therapy can be useful.

Whether or not a systematic exercise program is therapeutic is confusing for the post-polio patients who receive conflicting reports from their physicians, therapists or other patients. A study is planned to help clarify whether exercise in post-polio patients is beneficial or deleterious.

One group of epidemiologists at the Mayo Clinic in Rochester, Minnesota, who are receiving grant support from NINCDS for research in neuroepidemiology, have initiated some preliminary studies in the late effects of polio. These pilot investigations have been undertaken with the assistance of a grant from the National Easter Seal Society. The group was able to identify now living local patients who had suffered paralytic poliomyelitis during the period 1935 to 1955. Of the responders to a preliminary questionnaire survey, 20-25% reported recent deterioration in muscle function since the time of their maximal recovery from polio. Of further noteworthy interest is the finding also in this study that none of the responding patients reported signs of symptoms of amyotrophic lateral sclerosis (ALS). Conversely, none of the known ALS cases in the local area of this study had prior histories of acute paralytic poliomyelitis. These diseases appear not to be related. This research group plans to extend its preliminary survey studies to more extensive, controlled studies of the late effects of poliomyelitis.

The NINCDS Demyyelinating, Atrophic, and Dementing Disorders Program consulted with the Centers for Disease Control (Poliomyelitis Surveillance Program Office, Division of Immunization, Center for Prevention Services) in an attempt to identify other active research efforts in this area. The projects described in this report include all major research activities identified.

The NINCDS also supports an extensive program of basic research at grantee institutions throughout the nation through which scientists are gaining fundamental knowledge about nerves, muscles, and their interactions. Basic studies like these should produce the new information we need to develop rational research leads for postpolio muscular atrophy. As such leads develop and as the scientific community becomes more aware of the condition, we expect the number of research grant applications focused on postpolio muscular atrophy to increase.

Viral Clues Add to The ALS Puzzle

It's a disease without a cure, and also without a cause—at least a known one. The fatal neurodegenerative disease amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease, has been blamed on a wide variety of causes over the years, including genetic mutations in the enzyme superoxide dismutase (*Science*, 17 June, p. 1663), viral infection, and chemical exposure. No theory has conclusive proof behind it, but a new discovery adds some evidence for a potential viral role.

Researchers led by virologist Geoffrey Clements of Ruchill Hospital, Glasgow, Scotland, report in the 11 June issue of the *British Medical Journal* that they found evidence of infection with enterovirus—a family of viruses including poliovirus—in nine of 13 ALS cases. The team examined preserved spinal-cord specimens for sequences of RNA common to the 60-odd members of the enterovirus group. They found that one of two cases occurring within a family and eight of 11 cases occurring sporadically harbored the enterovirus RNA sequences. The six control patients did not have the sequences. Virologist Mark Pallansch of the Centers for Disease Control and Prevention in Atlanta says "this is a potentially significant finding," but warns that a larger sample needs to be studied.

Clements admits that no one knows how infection with an enterovirus—the second most common group of viruses in humans—might lead to ALS. Infection with poliovirus has been suggested to be a predisposing factor in ALS, and Clements says his result "keeps the viral theory alive." And his group intends to see if the virus sequences they are finding are abnormal. Clements speculates that an abnormal virus could escape the immune system and potentially cause damage. However, he notes that a viral role does not preempt other causative agents: "There may be multiple causes" of ALS, he says.