The Pathophysiology of Post-Polio Fatigue: A Role for the Basal Ganglia in the Generation of Fatigue.

Richard L. Bruno, et al.

Annals of the New York Academy of Sciences, 1995; 753: 257-275.

Abstract

Fatigue is the most commonly reported, most debilitating and least studied Post-Polio Sequelae (PPS) affecting the more than one million American polio survivors. Post-polio fatigue is characterized by subjective reports of problems with attention, cognition and maintaining wakefulness, symptoms reminiscent of nearly two dozen outbreaks during this century of post-viral fatigue syndromes that are related clinically, historically or anatomically to poliovirus infections. These relationships, recent studies that associate post-polio fatigue with clinically significant deficits on neuropsychologic tests of attention, histopathologic and neuroradiologic evidence of brain lesions and impaired activation of the hypothalamic-pituitary-adrenal axis, will be reviewed to described a role for the reticular activating system and basal ganglia in the pathophysiology of post-polio fatigue. The possibility of pharmacologic therapy for PPS is also discussed.

The Pathophysiology of Post-Polio Fatigue

A Role for the Basal Ganglia in the Generation of Fatigue. Fatigue is the most commonly reported, most debilitating and least studied Post-Polio Sequelae (PPS) affecting the more than 1.63 million American polio survivors with 91% reporting new or increased fatigue, 41% reporting fatigue significantly interfering with performing or completing work and 25% reporting fatigue interfering with self-care activities (1,2). Fatigue was reported to be triggered or exacerbated by physical overexertion in 92% and by emotional stress in 61%. Importantly, polio survivors differentiate between the physical tiredness and decreased endurance they associate with new muscles weakness, and a "brain fatigue" that is characterized by problems with attention and cognition. Between 70% and 96% of polio survivors reporting fatigue complained of problems with concentration, memory, attention, word-finding, maintaining wakefulness and thinking clearly, with 77% percent reporting moderate to severe difficulty with these functions (3).

Problems with attention and cognition suggest that the symptoms of post-polio fatigue cannot be explained merely by poliovirus-induced damaged to anterior horn motor neurons (4). Postmortem histopathology performed in the 1940s demonstrated the consistent presence of poliovirus lesions in specific brain areas. Brain stem centers were found to be "involved in even mild cases" of polio (5), with the midbrain reticular formation "always severely altered" (6) being "heavily peppered throughout" (7-11) with lesions that were "very common and often severe" (7). The hypothalamus, thalamic and caudate nuclei, putamen and globus pallidus were also lesioned by the poliovirus (11,12). Neurons in the periaquiductal gray, locus ceruleus, median raphe nuclei and especially the substantia nigra were also damaged or destroyed by the poliovirus (5, 8-11).

These findings indicate that poliovirus consistently and often severely damaged the brain areas responsible for cortical activation -- the reticular formation (13,14), hypothalamus (15), thalamus (16), locus ceruleus (17-20) -- i.e., the reticular activating system (RAS). And, clinical reports written during the polio epidemics corroborate the pathological evidence of poliovirus damage to the RAS since "drowsiness," lethargy, prolonged somnolence and even coma were described as sequelae of the acute poliovirus infection (7,12,21,22). Holmgren (23) reported that 34% of 258 patients with acute spinal, spinal/bulbar and non-paralytic demonstrated "mental changes" such as "disorientation, apathy, pronounced sleep disorder (and) irritability." These changes were significantly correlated with

abnormal slowing of the electroencephalogram (EEG) (i.e., the emergence of theta and some delta activity) in 42% of those with spinal or spinal and bulbar symptoms as well as in 33% of those with “non-paralytic” poliomyelitis. Meyer (24) reported that a "high percentage of children clinically recovered from poliomyelitis insofar as motor disability is concerned, reveal qualitative difficulties in mental functioning (such as) fatigability (sic) and fleeting attention" for months after the acute episode.

These reports of persistent drowsiness, fatigue and fleeting attention following the acute poliovirus infection are similar to polio survivors' recent complaints of late-onset fatigue and impaired attention (25). And, both acute and late-onset post-polio fatigue are reminiscent of nearly two dozen outbreaks during this century of post-viral fatigue syndromes (PFS) that are related clinically, historically or anatomically to poliovirus infections (26-28). These relationships and recent empirical comparisons between post-polio fatigue and chronic fatigue will be described in an attempt to understand the pathophysiology of post-polio fatigue.

Poliovirus and Fatigue

"Attenuated" Type II Poliovirus Infection and Impaired Cortical Activation. During the polio epidemics of the 1950's, a syndrome of impaired cortical activation and parkinsonism was attributed to the poliovirus. In 1951, three cases of "drowsiness" and rousable stupor, with marked slowing of the EEG, "bulbar signs" and parkinsonism were reported (29). While these symptoms were atypical of polio, their occurrence in an area where poliomyelitis had become a "serious problem," and the pathologic evidence that "the main brunt of the disorder was borne by the midbrain," prompted the authors to suggest that the syndrome might be caused by a poliovirus with "attenuated virulence." In 1952, 8 patients were described having an encephalitis whose dominant features were again somnolence and extrapyramidal symptoms (30). Type II poliovirus was isolated from half of the patients. The two fatal cases that came to autopsy had lesions in the reticular formation, hypothalamus and substantia nigra.

Magoun (31) stated it was "surprising" that parkinsonism was not a more common sequelae of all poliovirus infections because of the frequent and severe "injuries to the brain stem." Magoun explained what he called "this paradox" by invoking the correlation Bodian reported between the severity of poliovirus lesions in the reticular formation and basal ganglia: "If the injury to the lower brain stem reticular formation is intense, some of the vital centers are destroyed and the patient does not survive long enough for extrapyramidal symptoms to become displayed. If reticular injury is less intense, it may be below the threshold necessary to evoke (extrapyramidal) signs (page 250).” This correlation of lesion severity may explain why nearly all of the reported cases of post-polio parkinsonism have been rapidly fatal (32).

The association of poliovirus-induced somnolence with extrapyramidal symptoms highlights the prominence of poliovirus lesions in the basal ganglia and importance of the basal ganglia in maintaining cortical activation and attention. The basal ganglia are thought to gate "sensory input" to the thalamus (33) with the putamen said to control the "mechanisms that contribute to selective attention" (34). Putamen lesioned animals are "insensitive to quite gross visual stimuli" and "clearly (demonstrate) difficulty transferring attention from one object to another" (35). In humans, basal ganglia lesions and impairment of dopaminergic input to the striatum decrease both the diffuse activation of the cortex (36) and the ability to "maintain targeted attention" (37).

For example, Parkinson's disease (PD) patients demonstrate not only an impaired ability to "transfer attention" but also marked fatigue (38,39). "Excessive fatigue" was reported by 48% of PD patients (40) while nearly one-third reported that fatigue was their "most disabling symptom" (39). It is

noteworthy that one of the first descriptions of cognitive dysfunction in PD (41) could serve as a description of post-polio fatigue, i.e., a syndrome "characterized by a diminution of voluntary attention, spontaneous interest, initiative and the capacity for effort and work, with significant and objective fatiguability, and a slight diminution of memory" (38).

"Atypical" Poliomyelitis and Chronic Fatigue. Beginning in Los Angeles in 1934 and continuing for more than twenty years, there were more than a dozen outbreaks of a disease that was at first diagnosed as poliomyelitis, then as "abortive" or "atypical" poliomyelitis and finally named "Myalgic Encephalomyelitis" (ME) (26,42). Like poliomyelitis, initial symptoms of ME included headache, neck pain, low-grade fever and myalgia that often were followed by paresis. Irritability and anxiety, symptoms typical of the encephalitis accompanying bulbar polio (cf. 22) and even a few cases of post-acute parkinsonism (42) were also noted. Patients demonstrated hypersomnolence and "conspicuous changes in their levels of concentration" that persisted for months after the acute illness (26). Slowing of the EEG with the emergence of theta activity, similar to that documented in polio survivors, was also noted (44-46).

Unlike poliomyelitis, there were frequent complaints of numbness or parasthesias, usually no respiratory involvement, infrequent paralysis or muscle atrophy and almost invariably no fatalities. CSF protein was usually normal and poliovirus was never isolated from ME patients. Also unlike poliomyelitis, recovery from the acute symptoms of ME took just months (43). Most patients were left with a marked "exhaustion and fatiguability" that were "always made worse by exercise (and) emotional stress" (26). Patients continued to demonstrate fatigue, hypersomnolence, impaired concentration, reported "an inordinate desire to sleep," anomia, that they were "not as quick or incisive in thought as before, (had) a decreased ability to learn and a decline in their short-term memory" for years after the acute episode (26).

Despite the differences between poliomyelitis and ME, an association with the poliovirus was suggested by the fact that, of the more than one dozen ME outbreaks before the introduction of the injectable polio vaccine in 1952, nine occurred during or immediately after outbreaks of polio and several involved hospital staff who cared for polio patients (42,47-53).

Type III Poliovirus and Chronic Fatigue in Iceland. A more direct association between the poliovirus and ME was seen following a 1948 epidemic in Akureyri, Iceland. Patients presented with fever, myalgia and paresis and were at first diagnosed as having poliomyelitis. This diagnosis was quickly discarded as patients reported additional symptoms atypical of polio, including parasthesias, numbness, "nervousness" and "general tiredness" both acutely and for months after the acute episode. Also unlike poliomyelitis, there was a case fatality ratio of zero versus a minimum of 2.0% for polio in Iceland (54) and poliovirus was never isolated from any of these patients.

When patients were reexamined six years after the original outbreak, 72% reported chronic "nervousness and general tiredness" and 21% complained of "loss of memory" (55). Sigurdsson, et al (54) suggested two alternatives for the cause of this constellation of symptoms that he called "Akureyri Disease" but was more commonly referred to as "Iceland Disease" (ID): "Either a strain of poliomyelitis virus with unusual pathologic properties and of low virulence was responsible for this epidemic or, on the other hand, some unknown neurotropic virus has been present." Support for an "unusual" poliovirus as the cause came from Sigurdsson himself (56). There was an "extensive epidemic" of poliomyelitis caused by Type I poliovirus in Iceland during 1955 that coincided with and was followed by outbreaks of ID. Remarkably, two cities in which ID outbreaks were reported in 1955, as well as the area affected by the 1948 "Akureyri Disease" epidemic, were untouched by poliomyelitis. None of the children tested in the two ID-affected cities and only 13% of the children in

Akureyri showed antibodies to Type I poliovirus as opposed to 86% of the children tested in the polio epidemic areas. Further, following poliovirus immunization, children in one of the ID-affected cities demonstrated antibody titres to Type II and Type III poliovirus that were four and twenty-five times higher, respectively, than titers in a city where ID had not been reported. The authors concluded that Type I poliovirus was not related to the occurrence of ID but that inhabitants of the ID-affected areas had previously been exposed to an agent immunologically similar to Type III poliovirus.

An interesting coda to these findings is the report that when an American airman who had contracted polio in the 1955 Iceland epidemic returned to Massachusetts, a small outbreak of ID and polio occurred (57,58). More recent support for a relationship between poliovirus and ME came in 1989 when a "dangerously rising titre" to Type III poliovirus was documented in a patient who did not have polio but had been diagnosed with ME (59).

Post-Polio Fatigue and Chronic Fatigue Syndrome. A constellation of symptoms resembling ME was termed "Chronic Fatigue Syndrome" (CFS) following a Nevada outbreak in 1984 (27). Like ME and post-polio fatigue, CFS is characterized by complaints of chronic fatigue and impaired concentration that are triggered or exacerbated by physical exertion and emotional stress (59). Both CFS patients (59,60) and polio survivors (3) reported subjective memory impairment and word finding difficulty, while 85% of patients with CFS demonstrated "an excess of irregular slow wave activity" on EEG (61) similar to that seen following ME and polio (cf. 44-46). And, although polio survivors are on average at least ten years older than patients with CFS, the level of education, sex distribution, incidence of subjective difficulty with concentration and concomitant psychological symptoms were nearly identical in the two groups (2,27).

The recent emergence of CFS has allowed it to be studied using techniques that were unavailable during the polio, ME and ID epidemics and that now allow neuropsychologic, neuroanatomic and neuroendocrine comparisons between this most recent PFS and post-polio fatigue.

Empirical Comparisons of Post-Polio Fatigue and CFS

Neuropsychologic Studies. Some of the subjective difficulties with attention and cognition in CFS patients and polio survivors have been corroborated by the documentation of clinical abnormalities on neuropsychologic testing. CFS patients (62,63) and polio survivors with severe fatigue (25) have been shown to have clinical impairments of attention and information processing speed. Polio survivors reporting severe fatigue required 23% to 67% more time to complete tasks requiring sustained attention and vigilance than did polio survivors with no or mild fatigue (25). In spite of these marked impairments of attention, CFS patients (60) and polio survivors (2,25,64) have been shown to be within the high normal or superior range on measures of higher level cognitive processes and I.Q. and have higher than average levels of educational and professional achievement. Further, despite the high frequency of subjective complaints of memory impairment in CFS patients (65) and in 87% of polio survivors reporting fatigue (25), verbal memory has been shown to be intact on testing in both groups (25,63,66). However, polio survivors have twice been shown to have a clinical impairment of delayed recall of *visual* information whether or not they report fatigue (25).

These findings indicate that chronic fatigue is associated with impairments of attention and information processing speed but not of verbal memory or higher-level cognitive processes in patients with CFS and polio survivors. Given the histopathological documentation of frequent and severe poliovirus lesions in the brain's activating system, it was hypothesized that damage to the RAS and basal ganglia is responsible for both fatigue and impaired attention in polio survivors.

Neuroanatomic Studies. To test this hypothesis magnetic resonance imaging (MRI) of the brain was performed in hope of documenting evidence of poliovirus lesions in the RAS and basal ganglia. In a first study, small discrete and multiple punctate areas of hyperintense signal (HS) on MRI were imaged in the thalamus, caudate nucleus, centrum semiovale, deep and periventricular white matter in eleven of twelve polio survivors (3). These areas of HS were interpreted as evidence of poliovirus damage to the basal ganglia, RAS and its associated corticofugal white matter tracts. However, no attempt was made in this study to correlate HS with fatigue severity.

In a second study, 22 carefully selected polio survivors who had unequivocal histories of polio and were free from comorbidities that could have caused fatigue or cognitive problems underwent MRI of the brain (67). Areas of hyperintense signal in gray and white matter were imaged in 55% of subjects who rated their daily fatigue as moderate or higher but were not seen in any of the subjects reporting mild daily fatigue.

Small discrete areas of HS were imaged in the putamen, the rostral reticular formation and in the right medial leminiscus. Multiple punctate areas of HS were imaged in the periventricular and deep white matter and discrete areas of HS were seen in the centrum semiovale that were 5.0 mm^2 to 24.0 mm^2 in area. Subjects with and without HS were equal in terms of age, years of education, age at polio and the severity of acute polio. The presence of HS was significantly correlated with fatigue severity, year of acute polio and years since polio, but not with depressive symptoms, new respiratory problems or difficulty sleeping. The presence of HS was also significantly correlated with the frequency or severity of subjective problems with recent memory, thinking clearly, mind wandering, attention and concentration. The daily fatigue severity rating was significantly correlated with the frequency and severity of all of these cognitive problems.

These data support the hypothesis that areas of hyperintense signal are associated with late-onset fatigue and subjective problems with attention in polio survivors and may represent poliovirus damage within the brain activating system. HS imaged in the putamen and reticular formation most likely indicate areas where astroglia have replaced neurons destroyed during the acute poliovirus infection, since gliosis has been correlated with HS in postmortem examinations of the brains of healthy elderly adults (68). Damage to the putamen and caudate nucleus (16,17,18), and especially the reticular formation (69), has been shown in other populations to cause deficits in attention.

HS imaged along white matter tracts that have been implicated in the centrifugal spread of the poliovirus (70,71) may have resulted from damage to the brain parenchma by a local, tissue toxic effect of the poliovirus causing enlarged, fluid-filled spaces around arterioles (7), local neuronal atrophy (71; cf. 68,72) and possibly axonal demyelination (10,11). Diffuse atrophy and demyelination of axons within corticofugal white matter tracts could conceivably impair transmission, decrease cortical activation and cause attention deficits and other symptoms of fatigue. This notion is supported by a number of studies that have documented a relationship between HS, impaired attention and fatigue. Notably, periventricular and deep white (but not gray) matter HS have been imaged in 27% to 100% of CFS patients and have been suggested to represent either enlarged, fluid-filled spaces around arterioles or demyelination (27,68,72,73). White matter HS imaged in both demented (74,75) and non-demented (76-79) elderly adults have also been associated with impairments of attention and information processing speed similar to those documented in CFS patients and polio survivors with fatigue.

Neuroendocrine Studies. The correlation of HS on MRI with the symptoms of post-polio fatigue suggested that the effects of poliovirus on other brain centers might also be evident in polio survivors. The documentation of hypothalamic lesions on autopsy following polio suggested that

neuroendocrine abnormalities may also be post-polio sequelae. In 1992, Gupta, et al. reported a marked decrease in growth hormone secretion in polio survivors reporting muscle weakness (80). Since poliovirus lesions have been described in the arcuate nucleus (81) it is possible that damage to these neurons could result in decreased secretion of growth hormone releasing hormone (GHRH) with aging of the hypothalamus and thereby cause a decrease in GH release in mid-life (82). In addition, lesions in the paraventricular nucleus (PVN) were frequently documented following poliovirus infection (70) and are of special interest with regard to the symptoms of post-polio fatigue. PVN lesions could impair its ability to secrete corticotrophin releasing hormone (CRH) (83) and thereby decrease ACTH and cortisol release (see 84).

To examine the relationship between hypothalamic-pituitary-adrenal (HPA) axis activity and the symptoms of post-polio fatigue, polio survivors who underwent neuropsychological testing (25) had their plasma concentrations of cortisol and ACTH measured by a commercial laboratory using radioimmunoassay following a mild stressor (fasting) which is known to stimulate the HPA axis (85). Venous blood was drawn from an antecubital vein immediately upon subjects' 11:00 AM arrival at our laboratory after they has fasted for eleven hours, but preceding neuropsychological testing. Not surprisingly, mean plasma ACTH was elevated outside of the normal range (7.2 to 26.0 ng/ml) in the mild fatigue subjects (26.7 ± 3.2 ng/ml). In contrast, there was no ACTH elevation in subjects reporting severe daily fatigue (14.3 ± 0.6 ng/ml). Also, there was no difference in mean plasma cortisol levels between subjects reporting mild (11.5 ± 4.0 ug/dl) and severe (10.8 ± 1.2 ug/dl) fatigue, which were within the normal range (6.2 to 19.4 ug/dl) for 11:00 AM. These findings suggested that the HPA axis had been activated by the fasting stress in the mild fatigue subjects but not in those with severe daily fatigue who subsequently were found to have clinical impairments of attention and information processing speed on neuropsychological testing (25).

These pilot data lead to the measurement of plasma cortisol and ACTH in 44 patients evaluated by us following a similar fasting stressor: Venous blood was drawn from an antecubital vein immediately upon patients' 11:00 AM arrival at the laboratory after they has fasted for eleven hours. Patients with conditions that could have altered HPA axis activity (e.g., diabetes, hypothyroidism, administration of hormones) were excluded. Again, mean plasma ACTH was significantly elevated and outside of the normal range in subjects reporting mild daily fatigue (28.5 ±17.7 ng/ml) but not in those reporting high (i.e., moderate) fatigue (19.7±10.7 ng/ml) ($t=2.02$; $p<0.05$). Further, plasma ACTH was significantly positively correlated with the number of years since polio and significantly negatively correlated with the daily fatigue severity rating, the frequency of problems with recent memory, word finding and muscle weakness and the severity of problems with recent memory and staying awake during the day. Plasma cortisol levels were neither elevated nor different between subjects reporting mild (14.8 ± 5.7 ug/dl) and high daily fatigue (12.6 ±5.2 ug/dl), nor were cortisol levels correlated with demographic data or polio severity. However, plasma cortisol was significantly negatively correlated with the frequency of word finding difficulty and the severity of problems with recent memory. The severity of depressive symptoms as measured by the Beck Depression Inventory was not correlated with plasma cortisol or ACTH.

These data suggest that the HPA axis response to a fasting stressor is blunted in polio survivors reporting fatigue. This finding, coupled with histopathological evidence of poliovirus lesions in the PVN, suggest that the hyposecretion of ACTH may be secondary to decreased production of the hypothalamic secretalogs CRH and vasopressin whose cell bodies are located in the PVN. Further, the significant negative correlations between ACTH level and fatigue severity, cognitive problems and difficulty staying awake suggest that a diminution in HPA hormones may contribute to the symptoms of post-polio fatigue. An existing literature demonstrates that reduced levels of CRH and ACTH are

associated with fatigue and impaired attention, since both peptides exert "stimulatory effects on biochemical and electrophysiological parameters of the brain" (84,86). In man, administration of ACTH fragments lacking adrenal stimulating activity were associated with improved memory and alertness, "EEG arousal response patterns" and increased sustained attention that was "resistant to attentional fatigue" (87) plus a "statistically significant fall in fatigue" (88). These results were attributed to the direct activation of ACTH receptors on neurons in the hypothalamus, midbrain (89) and "the brain stem, particularly the non-specific reticular-thalamic system" (89,90). Thus, post-polio fatigue may be attributable to poliovirus lesions not only in the brain activating system but also in the PVN which reduce the secretion of neuromodulators that stimulate this system.

Decreased HPA activity has already been documented in patients with CFS and the reduced secretion of "activating" peptides such as CRH and ACTH has been implicated in its pathophysiology (91). Poteliakhoff (92) suggests that symptoms of chronic fatigue occur when "exhaustion of cells in the hypothalamus (leads) to decreased stimulation of the pituitary-adrenal axis." Such "exhaustion" could conceivably occur more easily in a hypothalamus whose aging PVN (and arcuate nucleus) neurons may have been lesioned and reduced in number by a previous viral infection.

It may be of importance to note that a reduction in CRH release would reduce plasma concentrations of not only ACTH but also ß-endorphin via a decrease in the secretion of their precursor, pro-opiomelanocortin (POMC). In addition, enkephalin secretion may also be reduced as a result of documented poliovirus damage to the periaquiductal gray (5,8). A reduction in ß-endorphin and enkephalin production might help to explain polio survivors' nearly doubled sensitivity to pain (3) as well as contribute to their impaired attention, since opioid peptides are thought to stimulate "the effort (to) pay attention" in animals with experimentally-induced attentional impairments (17).

Discussion

Taken together, the historical, clinical and empirical findings presented above suggest a model for the pathophysiology of post-polio fatigue:

- Poliovirus primarily and sometimes exclusively causes lesions in the reticular formation, basal ganglia and substantia nigra that have been associated with acute, post-acute and possibly chronic impairment of cortical activation, attention and subjective fatigue;
- Recent neuropsychologic data have documented impaired attention, while neuroradiologic and neuroendocrine data have indicated damage to brain areas responsible for cortical activation and attention in polio survivors and others with chronic fatigue;
- Therefore, poliovirus-induced damage to the brain's activating system may be responsible for decreasing cortical activation, impairing attention and generating the symptoms of post-polio fatigue.

While it is explicable that a poliovirus-lesioned brain activating system could cause acute impairment of cortical activation, inattention and fatigue, it is the recrudescence or seeming *de novo* appearance of these symptoms decades after the acute infection that require explanation. The emergence of late-onset post-polio fatigue may result from the age-related attrition of and changes in neurons that had survived the original polio infection. There is an age-related decrease in the number of substantia nigra neurons in human brain, with a mean loss of 33% of nigral neurons by age 50 (93). This age-related loss of nigral neurons, combining with an already diminished neuronal pool, is thought to be responsible for the emergence of postencephalitic parkinsonism (94). In addition, the cell bodies of animal reticular formation neurons distort and loose dendritic shafts with aging, abnormalities that resemble degenerative changes in the aging human cortex (95). Thus, the age-related attrition of

substantia nigra neurons and possible degeneration of reticular formation neurons, combining with an already decreased number of these neurons as a result of the original poliovirus infection, may impair the brain's activating system sufficiently to decrease cortical activation and produce impaired attention and fatigue as polio survivors reach mid-life (3).

A Role for the Basal Ganglia in Post-Polio Fatigue. The findings presented above suggest an integral relationship between poliovirus lesions in brain, impaired attention and fatigue (96). However, subjective difficulty with attention is neither the only nor even the most prominent symptom of fatigue. Polio survivors report that they are the most distressed and disabled by the "visceral" symptoms of fatigue: feelings of exhaustion, "passivity and an aversion to continued effort" (97) that generate an antipathy toward both mental and physical activity. However unpleasant and purposeless in polio survivors, feelings of passivity and aversion to activity have clear survival value, especially in organisms without conscious awareness that their attention and information processing speed are impaired. For example, an animal that continues to explore its environment even though its attention is impaired would be less able to direct attention on the goal of its exploration (e.g., searching for food) and would thereby waste already diminishing energy stores. More importantly, impaired attention could render the animal unaware of dangers in its environment (e.g., a predator stalking the animal in search of *its* food). Thus, there would be survival value in a brain mechanism that monitors cortical activation and biases the organism toward cessation of motor behavior and promotes rest when attention and information processing ability are impaired.

The basal ganglia are uniquely situated to monitor the level of cortical activation and stop an organism when its attention is inadequate to allow efficient and safe motor behavior. All parts of the cortex project to the dorsal striatum (the putamen and caudate nucleus) (16) which is said to "accumulate samples of ongoing cortical projected activity" (34). This cortical activity stimulates the striatum, whose discharge suppresses the chronic inhibition by the globus pallidus of the thalamus and, through it, cortical motor areas (98,99). It appears that "the natural function (of the dorsal striatum) is the facilitation of movement" (34) via disinhibiting the "automatic execution of learned motor plans" (99,100). A decrease in cortical activation could decrease stimulation of the putamen, reduce its "facilitory" input to the thalamus and thereby impair directed attention and prevent the cortical execution of learned motor behavior (101-103). This inhibition of the motor "activating set" may be subjectively perceived as the aversion to effort and passivity that accompany fatigue (33,34). Further, a reduction in the motor activating set might also generate two of the peripheral signs of central fatigue - the relaxation and lack of recruitment of motor units - that might underlie the visceral feeling of "exhaustion" that accompanies fatigue (104). In addition, the relaxation and reduced recruitment of motor units that may result from a decrease in the motor activating set would be accentuated by poliovirus-induced damage to the descending reticular activating system, since it is responsible for maintaining muscle tone in preparation for motor activity (17).

Implications for the Pharmacological Treatment of PPS. This putative role for the basal ganglia in the generation of fatigue suggests that stimulation of the basal ganglia via its dopaminergic afferents might increase cortical activation, counter attentional impairments, release the motor activating set and reduce both the cognitive and visceral symptoms of fatigue. Impairment of cortical activation and attention, disabling fatigue, as well as the bradykinesia and even akinesia that result from damage to dopaminergic afferents to the striatum in humans (36) can be reversed to some extent by the administration of L-Dopa or dopamine receptor agonists (103). A dopamimetic agent chosen to treat post-polio fatigue should not stimulate (as does amphetamine) or require the functioning of (as do L-Dopa, reuptake blockers and MAOIs) the remaining poliovirus-damaged dopaminergic neurons. We

are currently studying the use of bromocryptine, a post-synaptic dopamine receptor agonist, to treat post-polio patients whose fatigue has been been refractory to the current treatments of choice, i.e., adequate sleep and rest, energy conservation, the pacing of activities and reducing physical and emotional stress (3,105). However, there is the real danger that the pharmacological treatment of fatigue will allow polio survivors to resume their hyperactive Type A lifestyles, as they do now when their symptoms respond to current treatments, and further stress poliovirus-damaged, "metabolically vulnerable" neurons in the brain stem and anterior horn (105). Post-polio fatigue and all PPS must be treated holistically, with both physical and psychological factors being carefully considered when formulating a treatment strategy.

It is also possible that basal ganglia lesions may be related to other symptoms reported by polio survivors. Word finding difficulties are reported by 82% of polio survivors with fatigue (3) and appear similar both to word finding problems reported by CFS patients (60) and the "tip-of-the-tongue" phenomena in PD patients (106). In addition, 66% of polio survivors report generalized random myoclonus (GRM), the slow contraction or rapid twitching of hand, arm, trunk and leg muscles during sleep (2; cf. 21). GRM in polio survivors is reminiscent of the "periodic movements in sleep" seen in PD (107) that respond to treatment with dopamimetic agents (108).

We continue to study the possibility of basal ganglia abnormalities in polio survivors in an effort to understand the pathophysiology of post-polio fatigue and identify treatments for PPS.

References

1) Parsons, P.E. 1989. Data on polio survivors from the National Health Interview Survey. National Center for Health Statistics. Washington, D.C.
2) Bruno, R.L. & N.M. Frick. 1987. Stress and "Type A" behavior as precipitants of Post-Polio Sequelae. In Research and Clinical Aspects of the Late Effects of Poliomyelitis. L.S. Halstead and D.O. Wiechers, Eds. March of Dimes. White Plains, NY.
3) Bruno, R.L., N.M. Frick & J. Cohen. 1991. Polioencephalitis, stress and the etiology of post-polio sequelae. Orthopedics. 14:1185-93.
4) Trojan, D., D. Gendron & N.R. Cashman. 1991. Electrophysiology and electrodiagnosis of the post-polio motor unit. Orthopedics. 14:1353-1361.
5) Bodian, D. 1947. Poliomyelitis: Neuropathologic observations in relation to motor symptoms. J. Am. Med. Assoc. 134: 1148-1154.
6) Guizetti, H.U. 1933. Betrachtungen zur poliomyelitis des hirnstammes. Deutsch Ztschr f Nervenh. 131: 29-42.
7) Bodian, D. 1949. Histopathological basis of clinical findings in poliomyelitis. Am. J. Med. 6: 563-578.
8) Barnhart, M., R. Rhines, J.C. McCarter & H.W. Magoun. 1948. Distribution of lesions of the brain stem in poliomyelitis. Arch. Neurol. Psychiatry. 59: 368-377.
9) Matzke, H. A. & A.B. Baker. 1951. Poliomyelitis: A study of the midbrain. Arch. Neurol. Psychiatry. 65:1-15.
10) Peers, J.H. 1942. The pathology of convalescent poliomyelitis in man. Am. J. Pathol. 19: 673-695.
11) Luhan, J.A. 1946. Epidemic poliomyelitis: Some pathological observations on human material. Arch. Pathol. 42: 245-260.
12) Howe, H.A. & D. Bodian. 1942. Neural Mechanisms of Poliomyelitis. The Commonwealth Fund. New York, NY.
13) Morruzi, G. & H.W. Magoun. 1949. Brain stem reticular formation and activation of the EEG. EEG Clin. Neurophysiol. 1: 455-473.

14) Bentivoglio, M. & M. Steriade. 1990. Brainstemdiencephalic circuits as a structural substrate of the ascending reticular activation concept. In The Diencephalon and Sleep. M. Mancia & G. Marini, Eds. Raven Press. New York, NY.
15) Sakai, K., M. El Mansari, J.S. Lin, et al. 1990. The posterior hypothalamus in the regulation of wakefulness and paradoxical sleep. In The Diencephalon and Sleep. M. Mancia & G. Marini, Eds. Raven Press. New York, NY.
16) 16 Mesulam, M-M. 1985. Attention, confusional states, and neglect. In Principles of Behavioral Neurology. M-M. Mesulam, Ed. Davis. Philadelphia, PA.
17) Pribram, K.H. & D. McGuinness. 1992. Attention and para-attentional processing: Event-related brain potentials as tests of a model. Ann. NY Acad. Sci. 658: 65-92.
18) Jones, B.E. 1990. Influence of the brainstem reticular formation, including intrinsic mono-aminergic and cholinergic neurons, on forebrain mechanisms of sleep and waking. In The Diencephalon and Sleep. M. Mancia & G. Marini, Eds. Raven Press. New York, NY.
19) Robbins, T.W. 1986. Psychopharmacological and neurobiological aspects of the energetics of information processing. In Energetics and Human Information Processing. G.R.J. Hockey, A.W.K. Gaillard & M.G.H. Coles, Eds. Martinus Nijhoff. Dordrecht.
20) Mandell, A.J. 1980. Toward a psychobiology of transcendence. In The Psychobiology of Consciousness. J.M. Davidson & R.J. Davidson, Eds. Plenum. New York, NY.
21) Brown, J.R., A.B. Baker, I. McQuarrie, et al. 1947. The Bulbar form of poliomyelitis. J.A.M.A. 135: 425-428.
22) Baker, A.B. 1949. Neurologic signs of bulbar poliomyelitis. In Poliomyelitis. Lippincott. Philadelphia, PA.
23) Holmgren, B.E. 1952. Electro-encephalography in poliomyelitis. In Poliomyelitis. Lippincott. Philadelphia, PA.
24) Meyer, E. 1947. Psychological considerations in a group of children with poliomyelitis. J. Pediatrics. 31: 34-48.
25) Bruno, R.L., T. Galski, J. DeLuca. 1993. Neuropsychology of Post-Polio Fatigue. Arch. Phys. Med. Rehabil. 74: 1061- 1065.
26) Behan, P.O.& W.M.H. Behan. 1988. Postviral fatigue syndrome. C.R.C. Critical Reviews in Neurobiology. 4: 157- 178.
27) Buchwald, D.P.R., P.R. Cheney, D.L. Peterson, et al. 1992. A chronic illness characterized by fatigue, neurologic and immunologic disorders and active human herpesvirus type 6 infection. Ann. Int. Med. 116:103-113.
28) Hyde, B.M. 1992. Myalgic Encephalomyelitis (Chronic Fatigue Syndrome): An historical perspective. In The Clinical and Scientific Basis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. B.M. Hyde, J. Goldstein & P. Levine, Eds. The Nightingale Research Foundation. Ottawa, Ontario.
29) Bickerstaff, E.R. & P.C.P. Cloake. 1951. Mesencephalitis and rhombencephalitis. Brit. Med.J. 2:77-81.
30) Barrett, A.M., D. Gardner & A.M. McFarlan. 1952. An outbreak of encephalitis, possibly due to poliomyelitis virus. Brit. Med. J. 1:1317-1322.
31) Magoun, H.W. 1949. In Poliomyelitis. Lippincott. Philadelphia, PA. p. 250.
32) Duvoisin, R.C. & M.D. Yahr. 1965. Encephalitis and parkinsonism. Arch. Neurol. 12:227-239.
33) Heilman, K.M., K.K.S. Voeller & S.E. Nadeau. 1991. A possible pathophysiologic substrate of attention deficit hyperactivity disorder. J. Child Neurol. 6 (Suppl):S74-S79.
34) Denny-Brown, D. & N. Yanagisawa. 1976. The role of the basal ganglia in the initiation of movement. In The Basal Ganglia. M.D. Yahr, Ed. Raven. New York, NY.

35) Owen, A.M., A.C. Roberts, J.R. Hodges, et al. 1993. Contrasting mechanisms if impaired attentional set-shifting in patients with frontal lobe damage or Parkinson's disease. Brain. 116:1159-1175.
36) Echiverri, H.C., W.O. Tatum, T.A. Merens & S.B. Coker. 1988. Akinetic mutism. Pediatric Neurol. 4:228-230.
37) Bowen, F.P. 1976. Behavioral alterations in patients with basal ganglia lesions. Research Publications: Assoc. Res. Nerv. Ment. Dis. 55:169-180.
38) Brown, R.G. & C.D. Marsden. 1990. Cognitive function in Parkinson's disease. TINS. 1:21-28.
39) Friedman, J. & H. Friedman. 1993. Fatigue in Parkinson's disease. Neurology. 43:2016-2018.
40) Hilten, J.J. van, G. Hoogland, E.A. van der Velde, et al. 1993. Diurnal effects of motor activity and fatigue in Parkinson's disease. J. Neurol. Neurosurg. Psychiatry. 56:874-877.
41) Naville, F. 1922. Encephale. 17:369-375.
42) Acheson, E.D. 1959. The clinical syndrome variously called benign myalgic encephalomyelitis, Iceland Disease and epidemic neuromyasthenia. Am. J. Med. 26: 569-595.
43) Hyde, B.M. & S. Bergman. 1991. Chronic aspects of Akureyri Disease. In Post-Viral Fatigue Syndrome. R. Jenkins & J.F. Mowbray (Eds.). John Wiley & Sons. Chichester.
44) Ramsay, A.M. & E. O'Sullivan. 1956. Encephalomyelitis simulating poliomyelitis. Lancet. i: 762-767.
45) Galpine, J.F. & C. Brady. 1957. Benign myalgic encephalomyelitis. Lancet. i:757-758.
46) Daikos, G.K., S. Garzonis, A. Paleologue, et al. 1959. Benign myalgic encephalomyelitis. Lancet. i: 693-696.
47) Macrae, A.D. & J.F. Galpine. 1954. An illness resembling poliomyelitis observed in nurses. Lancet. ii: 350-352.
48) Gilliam, A.G. 1938. Epidemiological study of an epidemic, diagnosed as poliomyelitis, occurring among the personnel of the Los Angeles County General Hospital during the summer of 1934. U.S. Public Health Bull. (No. 240): 1-90.
49) Gsell, V.O. 1949. Abortive poliomyelitis. Helvetica Medica Acta. 3/4:169-183. 50 Fog, T. 1953. Vegetative (epidemic?) neuritis. Ugeskr. Laeg. 115: 1244-1248.
50) Fog, T. 1953. Vegetative (epidemic?) neuritis. Ugeskr. Laeg. 115: 1244-1248.
51) Pellew, R.A. 1951. Clinical description of a disease resembling poliomyelitis seen in Adelaide. Med. J. Aust. 1: 944-946.
52) White, D.N. & R.B. Burtch. 1954. Iceland Disease: A new infection simulating acute anterior poliomyelitis. Neurology. 4: 506-516.
53) Deisher, J.B. 1957. Benign myalgic encephalomyelitis (Iceland Disease) in Alaska. Northwest Med. 56: 1451-1456.
54) Sigurdsson, B., J. Sigurjonsson, H.J. Sigurdsson, et al. 1950. A disease epidemic in Iceland simulating poliomyelitis. Am. J. Hyg. 52:222-238.
55) Sigurdsson, B. and K.R. Gudmundsson. Clinical findings six years after outbreak of Akureyri Disease. Lancet. i: 766- 767.
56) Sigurdsson, B., M. Gudnadottir & G. Petursson. 1958. Response to poliomyelitis vaccination. Lancet. i: 370-371.
57) Hart, R.H. 1969. Epidemic neuromyesthenia. N. Eng. J. Med. 281:797.
58) Henderson, D.A. & A. Shelokov. 1959. Epidemic neuromyesthenia. N. Eng. J. Med. 260:757-764.
59) B.M. Hyde & A. Jain. 1992. Clinical observations of central nervous system dysfunction in post-infectious, acute onset M.E./CFS. In The Clinical and Scientific Basis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. B.M. Hyde, J. Goldstein & P. Levine, Eds. The Nightingale Research Foundation. Ottawa, Ontario.

60) Altay, H.T., B.B. Toner, H. Brooker, et al. 1990. The neuropsychological dimensions of postinfectious neuromyesthenia. Int'l. J. Psychiatry in Med. 20:141-149.
61) Jamal, G.A. 1992. Evidence for organic disturbance in Post Viral Fatigue Syndrome. In The Clinical and Scientific Basis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. B.M. Hyde, J. Goldstein & P. Levine, Eds. The Nightingale Research Foundation. Ottawa, Ontario.
62) DeLuca, J., S.K. Johnson & B.H. Natelson. 1993. Information processing efficiency in chronic fatigue syndrome and multiple sclerosis. Arch. Neurol. 50: 301-304.
63) Sandman, C.A., J.L. Barron, K. Nackoul, et al. 1993. Memory deficits associated with chronic fatigue immune dysfunction syndrome. Biol. Psychiatry. 33:618-623.
64) Lonnberg, F. 1993. Late onset polio sequelae in Denmark. Scand. J. Rehab. Med. Suppl. 28: 1-32.
65) McDonald, E., H. Cope & A. David. 1993. Cognitive impairment in patients with chronic fatigue. J. Neurol Neurosurg Psychiatry. 56:812-815.
66) Graffman, J., V. Schwartz, J.K. Dale, et al. 1991. Analysis of neuropsychological functioning in patients with chronic fatigue syndrome. J. Neurol. Neurosurg. Psychiatry. 56:684- 689.
67) Bruno, R.L., J. Cohen, T. Galski & N.M.Frick. 1994. The neuroanatomy of post-polio fatigue. Arch. Phys. Med. & Rehabil. 75:498-504.
68) Awad, I.A., P.C. Johnson, R.F. Spetzler & J.A. Hodak. 1986. Incidental subcortical lesions identified on magnetic resonance imaging in the elderly (II). Stroke. 17:1090-1097.
69) Parasuraman, R. & P. Nestor. 1986. Energetics of attention and Alzheimer's Disease. In Energetics and Human Information Processing. G.R.J. Hockey, A.W.K. Gaillard & M.G.H. Coles, Eds.Martinus Nijhoff. Dordrecht.
70) Howe, H.A. & D. Bodian. 1941. Neuropathological evidence on the portal of entry problem in human poliomyelitis. Bull. Johns Hopkins Hosp. 69: 183-214.
71) Bodian, D. & H.A. Howe. 1941. Neurotropism and the genesis of cerebral lesions in poliomyelitis. Bull Johns Hopkins Hosp. 68: 58-76.
72) Kirkpatrick, J.B. & L.A. Hayman. 1987. White-matter lesions in MR imaging of clinically healthy brains of elderly subjects: Possible pathological basis. Radiology. 162:509- 511.
73) Daugherty, S.A., B.E. Henry, D.L. Peterson, et al.. 1991. Chronic fatigue syndrome in northern Nevada. Rev. Infect. Dis. 13 (Suppl 1):S39-44.
74) Almkvist,O., L-O. Wahlund, G. Anderson-Lundman, et al. 1992. White-matter hyperintensity and neuropsychological functions in dementia and healthy aging. Arch. Neurol. 49:626-632.
75) Kertesz, A., M. Polk & T. Carr. 1990. Cognition and white matter changes on magnetic resonance imaging in dementia. Arch Neurol. 47:387-391.
76) Austron, M.G., R.F. Thompson, H.C. Hendrie, et al. 1990. Foci of increased T2 signal intensity in MR images of healthy elderly subjects: A follow-up study. J. Am. Geriatr. Soc. 38:1133-1138.
77) Boone, K.B., B.L. Miller, I.M. Lesser, et al. 1992. Neuropsychological correlates of white-matter lesions in healthy elderly subjects. Arch. Neurol. 49:549-554.
78) Junque, C., J. Pujol, P. Vendrell, et al. 1990. Leukoaraiosis on magnetic resonance imaging and speed of mental processing. Arch Neurol. 47:151-156.
79) Gupta, S.R., M.H. Naheedy, J.C. Young, et al. 1988. Periventricular white matter changes and dementia. Arch. Neurol. 45:637-641.
80) Gupta, K.L., K.R. Shetty, I.W. Rudman & D. Rudman. 1992. Impaired nocturnal growth hormone secretion with age in post-polio syndrome. Clin. Res. 40:688.
81) Neubuerger, K.T. 1949. Bulbar poliomyelitis. In Poliomyelitis. Lippincott. Philadelphia, PA.
82) Rao, U., K.R.Shetty, D.E. Mattson, et al. 1993. Prevalence of low plasma IGF-I in poliomyelitis survivors. J. Am. Geriatric Soc. 41:697-702.

83) Petrusz, P & I. Merchenthaler. 1992. The corticotropinreleasing factor system. In Neuroendocrinology. C.B. Nemeroff, Ed. CRC Press. Boca Raton, FL.
84) Meyerhoff, J.L., E.H. Mougey & G.J. Kant. 1987. Paraventricular lesions abolish the stress-induced rise in pituitary cyclic AMP and attenuate the increases in plasma levels of proopiomelanocortin-derived peptides and prolactin. Neuroendocrinology. 46:222-230.
85) Dallman, M.F., A. Strack, S. Akana, et al. 1993. Feast and famine: Critical role of glucocorticoids with insulin in daily energy flow. Frontiers in Neuroendocrinology. 14: 303-347.
86) Moodradian, A.D. 1992. Geriatirc Neuroendocrinology. In Neuroendocrinology. C.B. Nemeroff, Ed. CRC Press. Boca Raton, FL.
87) Miller, L.H., A.J. Kastin, C.A.Sandman, et al. 1974. Polypeptide influences on attention, memory and anxiety in man. Pharm. Biochem. & Beh. 2: 663-668.
88) Reinberg, A., L. Briere, G. Fraboulet, et al. 1981. Clinical chronobiology of ACTH 1-17. Chronobiologia. 8: 101-115.
89) Strand, F.L., A. Cayer, E. Gonzalez & H. Stoboy. 1976. Peptide enhancement of neuromuscular function. Pharm. Biochem. & Beh. 5 (Suppl. 1): 179-187.
90) VanWimersma Greidanus, Tj. B. & D. de Wied. 1971. Effects of systemic and intracerebral administration of two opposite acting ACTH-related peptides on extinction of conditioned avoidance behavior. Neuroendocrinology. 7:291- 301.
91) Demitrack, M.A., J.K. Dale, S.E. Straus, et al. 1991. Evidence for impaired activation of the hypothalamicpituitary-adrenal axis in patients with chronic fatigue syndrome. J. Clin. Endocrinology & Metabolism. 73: 1224- 1234.
92) Poteliakhoff, A. 1981. Adrenocortical activity and some clinical findings in acute and chronic fatigue. J. Psychosom. Res. 25:91-95.
93) Mann, D.M.A., P.O. Yates & J. Hawkes. 1983. The pathology of the human locus ceruleus. Clinical Neuropathology. 2: 1-7.
94) Vincent, F.M. & W.G. Myers. 1978. Poliomyelitis and Parkinsonism. N. Engl. J. Med. 298: 1122.
95) Machado-Salas, J., M.E. Scheibel, A.B. Scheibel. 1977. Neuronal changes in the aging mouse: Spinal cord and lower brain stem. Exp. Neurol. 54: 504-512.
96) Kennedy, H.G. 1988. Fatigue and fatiguability. Br. J. Psychiatry. 153:1-5.
97) Hockey, G.R.J. 1986. Changes in operator efficiency as a function of environmental stress, fatigue and circadian rhythms. In Handbook of Perception and Human Performance. K.R. Boff, L. Kaufman & J.P. Thomas, Eds. Vol 2. John Wiley & Sons. New York, NY.
98) Alexander, G.E., M.R. DeLong & P.L. Strick. 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Ann. Rev. Neurosci. 9:357- 381.
99) Strange, P.G. 1993. Dopamine receptors in the basal ganglia. Movement Disorders. 8:263-270.
100) Marsden, C.D. & J.D. Parkes. 1981. "On and off" variability and response swings in Parkinson's disease. In Research Progress in Parkinson's Disease. F. Clifford-Rose & R. Capildeo, Eds. Pitman. London.
101) Oades, R.D. 1985. The role of noradrenaline in tuning and dopamine in switching between signals in the CNS. Neuroscience & Beh. Revs. 9:261-282.
102) Panksepp, J. 1982. The pleasure in brain substrates of foraging. Behav. & Brain Sci. 5:71-72.
103) Alexander, G.E., M.D. Crutcher & M.R. DeLong. 1990. Basal ganglia-thalamocortical circuits. In Progress in Brain Research. H.B.M. Uylings, C.G. Van Eden, J.P.C. De Bruin, et al., Eds. 85: 119-146.
104) Edwards, R.H.T. 1981. Human muscle function and fatigue. In Human Muscle Fatigue. Ciba Foundation Symposium 82. Pittman. London.

105) Bruno, R.L. & N.M. Frick. 1991. The psychology of polio as prelude to Post-Polio Sequelae. Orthopedics. 14: 1185-1193.
106) Matison, R., R. Mayuex, J. Rosen & S. Fahn. 1982. "Tip-of -the-tongue" phenomenon in Parkinson disease. Neurology. 32:567-570.
107) Weiner, W.J. & A.E. Lang. 1989. Movement Disorders. Futura. Mount Kisco, N.Y. p. 51-54.
108) Brodeur, C. J. Montplaisir, R. Godbout & R. Marinier. 1988. Treatment of restless legs syndrome and periodic movements during sleep with L-Dopa. Neurology. 38:1845-1848.