FROM
The Post-Polio Institute
and
The International Centre for Post-Polio Education and Research
postpolioinfo@aol.com

Orthopedics, 1991; 14 (11): 1269-1276.

POLIOENCEPHALITIS, STRESS AND THE ETIOLOGY OF POST-POLIO SEQUELAE

Richard L. Bruno, Nancy M. Frick, and Jesse Cohen.

ACKNOWLEDGEMENTS

This paper is dedicated to David Bodian, M.D. This research was supported by grants from the George Ohl Foundation. The authors gratefully acknowledge the criticism of Dr. Robert Sapolsky and the expertise and tireless efforts of Mary Ann Solimine, R.N., M.L.S., without whom this work would not have been possible.

ABSTRACT

Post-mortum neurohistopathology from 158 individuals who contracted polio before 1950 are reviewed that document polio virus-induced lesions in reticular formation, hypothalamic, thalamic, peptidergic and monoaminergic neurons in the brain. This polioencephalitis was found to occur in every case of poliomyelitis, even those without evidence of damage to spinal motor neurons. These findings,

in combination with data from the 1990 National Post-Polio Survey and new magnetic resonance imaging studies documenting post-encephalitis-like lesions in the brains of polio survivors, are used to present hypotheses that polioencephalitic damage 1) to aging reticular activating system and monoaminergic neurons is responsible for post-polio fatigue and 2) to enkephalin-producing neurons is responsible for hypersensitivity to pain in polio survivors. Hypotheses are also presented that the anti-metabolic action of glucocorticoids on polio-damaged, metabolically vulnerable neurons is responsible for the fatigue and muscle weakness reported by polio survivors during emotional stress. Suggestions for the treatment of Post-Polio Sequelae based on these hypotheses are also presented.

"In spite of much evidence opposing such a view, there appears to be at least the popular impression that the only symptomatically important injury to the nervous system associated with poliomyelitis is the decrease in motor neuron collections" (1).

This statement made in 1948 is still an accurate description of the current thinking about the pathophysiology of poliomyelitis. Yet, as early as 1884, clinicians were relating the symptoms of polio not only to damage of spinal cord neurons but also to polio virus lesions in the brain (2). Today, we must look back to studies performed during the polio epidemics and look beyond the anterior horn if we are to fully understand the etiology of Post-Polio Sequelae (PPS).

The purpose of this paper is to 1) present neurohistopathological data collected during the polio epidemics and new radiographic findings to describe the location and extent of polio virus-induced damage in the brain, 2) use these findings in combination with data from the 1990 National Post-Polio Survey to formulate hypotheses about the etiology of post-polio fatigue, pain, muscle weakness and stress-induced symptoms and 3) suggest treatments for PPS based on these hypotheses.

POLIOENCEPHALITIS and CNS LESIONS

The most incisive and insightful studies of the supraspinal activities of the polio virus are those of David Bodian. Fifty years ago, Bodian performed histopathology on both lower primates experimentally inoculated with the polio virus and humans who came to autopsy following poliomyelitis to identify the portal of entry of the polio virus. In doing so, Bodian mapped the lesions caused by the virus from the spinal cord to the cortex. His findings revealed that the polio virus was not a "silver bullet" aimed only at anterior horn motor neurons, but that the virus caused widespread but consistently placed lesions throughout the central nervous system (CNS). He concluded that poliomyelitis was actually an afterthought of the polio virus, with the primary site of viral activity and neuronal lesions being the brain:

All the evidence available shows conclusively that every case of poliomyelitis, human or experimental, exhibits lesions of

the brain. In the experimental animal this includes non-paralytic and abortive cases as well as paralytic cases. Some animals with non-paralytic poliomyelitis do not have lesions in the spinal cord but have a characteristic distribution of lesions in the brain (3).

It seems likely that in all cases of poliomyelitis...an encephalitis exists whether symptoms are present or not. Neuronal and inflammatory lesions may be regularly found in any susceptible center... in individuals who have never exhibited symptoms (4). As far as the pathologist is concerned, all cases of poliomyelitis are encephalitic (3).

Bodian and other researchers consistently documented polio virus-induced lesions in certain brain areas while noting the consistent absence of lesions in others: polioencephalitis "may be of greater or less severity (from case to case), but the distribution of lesions in susceptible centers varies but little" (5). Table 1 lists the frequency and severity of brain lesions seen in autopsies of 158 polio patients. Brain stem centers were found to be "involved in even mild cases" (3). As early as 1933, Guizetti (6) stated that "only one area is always severely altered, and that is the so-called substantia reticularis." The substantia reticularis, or reticular formation, was found by Bodian to be "heavily peppered throughout" with lesions described as "very common and often severe" (4)(Figure 1). Other researchers also documented these frequent and severe lesions (1,7,8) with Luhan (9) describing the reticular formation as the "most

uniformly involved" brain center following polio infection.

Moving dorsally in the brain stem, the vestibular (1,3) and cerebellar roof nuclei (5,7) were found to be the next most severely affected centers. It is important to note Bodian's statement that in "patients who had no bulbar signs, and in whom death was due to... complications unrelated to poliomyelitis infection, we found...the only centers consistently showing severe damage were the reticular formation and the vestibular nuclei" (10). It appears that damage to these areas was a consequence of all polio infections regardless of their severity and occurred "whether (clinical) symptoms are present or not" (5).

Moving rostrally, the next most severely affected center was found to be the periaquiductal gray (1,3) whose neurons have more recently been identified as producing the opioid peptide enkephalin (11). Other brain stem neurons that produce neurotransmitters were also found to be damaged by the polio virus. The locus ceruleus, center of origin for noradrenergic fibers, was said by Luhan (9) to be the brain center "most hard hit" by the polio virus. Several studies found that the dopamine-producing substantia nigra was damaged (3,7,8,9) as were the serotonergic median raphe nuclei (8).

Hypothalamic nuclei were also found to be damaged, with "severe" lesions seen in some cases (4). Bodian (3) documented lesions in both the paraventricular nucleus and preoptic area while Luhan (9) documented hypothalamic

lesions that he thought were more severe in posterior regions. Lesions were also noted in lateral, median and midline thalamic nuclei and the septal nuclei (5).

Cortical lesions, while frequent and severe, were limited only to the motor and pre-motor areas (4,5). It is important to note that all other cortical areas were completely unaffected by the polio virus. For example, even when directly inoculated into the occipital cortex, the polio virus was unable to infect these non-motor neurons (12,13). The inability of the polio virus to damage other cortical regions left higher-order cognitive processes intact and allowed polio survivors to attain levels of social, educational and professional achievement far higher than those of the general population (14).

Magnetic Resonance Imaging of Polioencephalitic Lesions. In an attempt to document polioencephalitic lesions in survivors of paralytic polio, magnetic resonance imaging (MRI) of the brain was performed on 12 subjects. White matter scarring characteristic of post-encephalitic gliosis was seen in 92% (11) of the subjects. Similar lesions may be seen in only 1-2% of age-matched controls. Gray matter lesions in the reticular formation or lateral thalamic nuclei were seen in 17% (2) of those studied. The individual with reticular formation lesions reported the most severe fatigue in this series, fatigue that had forced her to stop working and accept Social Security disability payments. Additional data is being collected to document the relationship between

the location of brain lesions and PPS fatigue. However, these preliminary data do support the histopathological findings of polioencephalitis in non-fatal paralytic polio and are evidence of polio virus-induced damage to reticular formation and thalamic neurons.

The relatively low incidence of detectable gray matter lesions and the high frequency of white matter lesions requires explanation. First, because of limited MRI resolution, the ability to visualize gray matter lesions is restricted to those cases in which there are clearly delineated areas of neuron destruction and gliosis greater than 1 mm. in diameter. Even the extensively damaged reticular formation was said to be "heavily peppered throughout (with lesions) rather than being predominately composed of large discrete areas of destruction" (4). Bodian (4) reported only a few cases in which lesions were seen "as large as 1 or 3 mm. in diameter."

Second, not all neurons that evidence lesions in the acute and post-acute stages are destroyed by the polio virus. Bodian (15) suggests that approximately 50% of motor neurons infected by the polio virus are destroyed. Thus, because of the scattering and small size of the areas of neuronal destruction and the percentage of neurons destroyed by the polio virus, imaging of gray matter lesions with MRI may be infrequent.

With regard to the white matter lesions, the areas in which they were imaged contain cortico-spinal (cerebral peduncle,

centrum semiovale) and thalamo-cortical radiations that have been implicated in the centrifugal spread of the polio virus (13). Lesions along these fiber tracts may result from the reaction of tissues other than gray neurons to the passage of the polio virus or the virus' entrance into susceptible tissues.

For example, lymphocytic infiltrations following the acute polio infection were said to "sometimes reach massive proportions" and be "present diffusely in the tissue for two or three weeks, but persist as perivascular accumulations as late as the second month" (10). Bodian suggested that the combination of a "severe reaction to virus and local circulatory embarrassment" may be responsible for tissue damage seen in other than gray neurons following polio infection, just as it is thought to cause damage:

....frequently described in other viral encephalitides. It is alsoconceivable that in small areas an unusually high concentration of virus may produce a toxic effect apart from the ordinary pathologic effect (on gray) nerve cells. Such toxic effects of influenza virus have been described (4).

Thus, damage caused by the "cuffing" of blood vessels by lymphocytes, local ischemia and a tissue toxic effect of the polio virus may combine to produce the white matter lesions imaged. However, only the correlation of post-mortum histology with MRI findings will define the nature of these lesions.

This histological and MRI evidence of lesions indicates that the polio virus both damaged and destroyed neurons in CNS territories beyond the anterior horn. These findings allow hypotheses to be formulated about the etiology of PPS, especially those symptoms that cannot be explained by poliomyelitic-damage to the motor unit, such as fatigue and pain. Further, polioencephalitic lesions in the brain may help to explain the report of PPS symptoms by 28% of the more than 820,000 survivors of non-paralytic polio (16).

Polioencephalitis and Post-Polio Fatigue

Unaccustomed fatigue is the most commonly reported, most debilitating, least studied and most poorly understood PPS. In the 1985 National Survey of 676 polio survivors, 91% reported new or increased fatigue (17). Fatigue was also reported to be the most disabling of PPS, significantly interfering with social activities in 13% of respondents, with self-care in 25% and with completing or performing work in 41%. The 1990 National Survey of 373 polio survivors documented that 12% of respondents who reported new fatigue without new muscle weakness were not working or were on disability, as compared with only 2% of those reporting new muscle weakness without new fatigue.

Etiology of PPS Fatigue. The first study of the etiology of PPS fatigue was performed by Owen and Jones. (18) They assessed cardiopulmonary conditioning in post-polio subjects and found a "level of cardiac fitness comparable to (that in) patients after recent myocardial infarction." They

concluded that post-polio fatigue may be related to cardiopulmonary deconditioning since it is "quite similar to (fatigue) seen in deconditioned individuals with chronic pain syndrome."

The subjects in this study were significantly different from the post-polio patients with fatigue treated on this service, many of whom report a severe and malignant fatigue and not just "moderate problems with fatigue and endurance" (18). Where Owen and Jones (18) subjects' reported fatigue following "5 to 7 minutes of exercise," our patients cannot exercise for one minute without experiencing fatigue. Further, post-polio fatigue is more than the physical 'tiredness' and shortness of breath that are reported by chronic pain patients. As one polio survivor described her fatigue, "I get a very drowsy feeling, as if I were drugged. When I have things to do, I get very flustered and stressed and then I can't organize my mind to get the job done. Even when I sleep for ten hours, I never feel as if I'm rested. My brain always feels tired."

Respondents to the 1990 National Post-Polio Survey reporting new fatigue also described "brain tiredness," reporting difficulty with concentration (96%), memory (85%), attention (82%), word finding (80%), maintaining wakefulness (71%) and thinking clearly (70%). Seventy-seven percent of respondents reported moderate to severe difficulty with these cognitive functions.

Post-Polio Fatigue and the Reticular Activating System

These data suggest that post-polio fatigue is related less to physical deconditioning and more to an impairment in the brain's ability to activate itself. This suggestion should not be surprising given the location and severity of polioencephalitic lesions in the reticular formation, posterior hypothalamus and thalamus - the brain's Reticular Activating System (RAS)(Figure 2).

The reticular formation is a net-like arrangement of brain stem neurons that receive input from all sensory systems (19,20,21). Sensory stimuli enter the reticular formation and activate the thalamus, via the posterior hypothalamus, causing desynchronization of cortical neurons and 'alerting' the cortex to begin processing the ascending sensory information (22,23). Neurons in the locus ceruleus and substantia nigra are thought to stimulate the RAS and promote cortical arousal through their respective release of norepinephrine (24) and dopamine (25,26,27).

It has long been known that severe damage to RAS centers can prevent cortical arousal and thereby cause irreversible coma (28). Polioencephalitic damage to the RAS following the acute polio infection was reported to cause coma, but also was associated with less severe symptoms such as "disorientation," "drowsiness" (4) and "prolonged somnolence" (29). Meyer (30) noted 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 and fleeting attention" for months after the acute polio infection. She stated that these symptoms were "particularly evident" when there was acute "encephalitic involvement" and were present "to some degree (where) the medical history notes drowsiness, severe headache, and, in some instances, only nausea at the onset."

These clinical observations suggest that polioencephalitic lesions impaired the ability of the RAS to maintain a state of alert wakefulness, activate the cortex and arouse the brain to effectively process information both acutely and for months after the acute polio infection. It is hypothesized that PPS fatigue, characterized by impairments in arousal, attention, cognition and memory, also results from polioencephalitic lesions in the RAS and associated brain-stem centers impairing the mechanism of cortical arousal. The emergence of PPS fatigue thirty or more years after the acute polio infection may result from age-related changes in and possibly the death of neurons that had been damaged by, but survived, the acute polio virus infection.

Machado-Salas, et al. (31) described reticular formation neurons in aged mice as having distorted cell bodies and a marked loss of dendritic shafts - abnormalities that the authors state resemble degenerative changes in the aging human cortex. Mann, et al. (32) documented age-related decreases in the number of locus ceruleus neurons in humans beginning at about age 35. McGeer, et al. (33)

documented age-related decreases in the number of substantia nigra neurons in the human brain, with a mean loss of 33% of nigral neurons by age 50. The age-related loss of substantia nigra neurons, combining with an already diminished neuron pool, is thought to be responsible for the emergence in mid-life of Parkinson's Disease, another putatively postencephalitic disorder (34).

Age-related degeneration of reticular formation neurons and the attrition of locus ceruleus and substantia nigra neurons, combining with an already decreased number of neurons in these areas as a result of the original polio infection, are hypothesized to impair the RAS sufficiently to decrease cortical activation and produce symptoms of PPS fatigue as polio survivors reach mid-life (Figure 2).

Stress and Post-Polio Fatigue

Any hypothesis concerning the pathophysiology of PPS must explain the finding that emotional stress was reported to be the second leading cause of PPS (17). Sixty-one percent of respondents to the 1985 National Survey reported that emotional stress caused fatigue (17). In the 1990 National Survey, significantly more of the respondents who reported new fatigue also reported symptoms of anxiety (Table 2). Also, respondents who reported fatigue had significantly elevated Type A and Sensitivity to Criticism and Failure scores on the Reinforcement Motivation Survey (RMS) as compared to those without fatigue (35,36). Further, the severity of fatigue was significantly correlated with

symptoms of anxiety, the two RMS scores and respondents' reports that emotional stress increased PPS symptoms.

Emotional stress has been found to induce symptoms similar to those associated with PPS fatigue in non-disabled individuals. An emotional stressor ("dealing with difficult or helplessly ill patients") was reported to be the most frequent cause of fatigue in a survey of 1801 nurses (37). Empirically, subjects who described a sustained vigilance task as stressful reported an impaired ability to maintain attention, decreased energy, increased fatigue and drowsiness - symptoms that were correlated with the release of glucocorticoids (38). And, it is glucocorticoids that are thought to be the chemical link between emotional stress and symptoms of fatigue.

In humans, the administration of high-dose glucocorticoids has been shown to decrease attention, concentration and mental speed (39). Elevated glucocorticoid plasma levels have been associated with increased signal detection thresholds (40) while elevated but still physiological plasma levels of cortisol were associated with reduced cortical activation and decreased sensitivity to changing stimuli (41). Glucocorticoids are thought to produce these effects by generally inhibiting neuronal activity in the brain (40) and by specifically impairing the ability of RAS to focus attention (42) through the activation of glucocorticoid receptors on RAS neurons.

Glucocorticoid receptors have been demonstrated in animals on reticular formation (43), thalamic (44), locus ceruleus and substantia nigra neurons (45). Glucocorticoids have been shown in animals to specifically decrease the firing rate of reticular formation neurons (46,47) and decrease glucose utilization in locus ceruleus neurons by at least 25% (48). Glucocorticoids are thought to generally interfere with neuronal glucose uptake, inhibit protein synthesis and deplete neuronal energy reserves (43). Neurons that survived the original polio virus infection would be especially susceptible to disruption of their metabolism because of polio virus-induced damage to the metabolic apparatus (endoplasmic reticulum, Golgi net), alterations in oxidative metabolism and protein synthesis (49) and the impairment of axonal transport of trophic factors in polio-damaged neurons (50).

Thus, it is hypothesized that the anti-metabolic effect of glucocorticoids secreted during stress inhibits the firing of the remaining, degenerated reticular formation neurons and remaining locus ceruleus and substantia nigra neurons. This decrease in neuronal firing inhibits the ability of the RAS to activate the cortex and thereby triggers or exacerbates symptoms of PPS fatigue. Since Type A behavior has been associated with a hyperactive and slowly recovering endocrine response to stress (51,52), the elevated Type A scores in polio survivors reporting PPS fatigue suggest that they may produce an accentuated and prolonged glucocorticoid response to stress. Such a response would

amplify and prolong the anti-metabolic action of glucocorticoids on CNS neurons and could explain patients' reports that PPS fatigue often lasts for days after an emotionally stressful situation has ended.

Stress and Post-Polio Muscle Weakness

The hypothesized relationship between stress, glucocorticoids and PPS may also help to explain the report of stress-induced muscle weakness in 55% of respondents to the 1985 National Survey (17). Stress in animals has been shown to accelerate the onset of muscle fatigue (57) and augment age-related decreases in the number of terminal axon branches (58). Again, glucocorticoids may be the mediators of these stress-induced impairments. Glucocorticoid receptors have been demonstrated in animals on spinal motor neurons (59) and elevated glucocorticoid levels have been associated with the inhibition of axonal sprouting in motor neurons of aged animals with experimental motor nerve denervation (60). These effects may result from glucocorticoid-induced inhibition of glucose utilization and the impairment of neuronal metabolism.

Bodian suggested that post-polio motor neurons "may be vulnerable for life to metabolic factors such as changes of senescence" (15) since their metabolic apparatus was altered by the polio virus and because the axons of surviving damaged motor neurons are extensively sprouted (49). Wiechers (61) suggested that PPS muscle weakness emerges as these "metabolically vulnerable" motor neurons fail to

function, lose axonal sprouts and even die because they "are just not able to keep pace with the metabolic demands of innervating all of their muscle fibers." Stress-induced muscle weakness may result from glucocorticoids further impairing metabolism and preventing already compromised neurons from activating their excessively sprouted but progressively decreasing motor unit territories.

Polioencephalitis and Pain

It was noted above that neurons in the periaquiductal gray were found by Barnhart, et al. (1) and Bodian (3) to have been damaged by the polio virus. Neurons in the substantia gelatinosa (lamina II of the spinal cord's posterior horn) were also found by these researchers to be damaged following polio infection. Both periaquiductal gray and substantia gelatinosa neurons produce the opioid peptide enkephalin (11).

Polio virus-induced destruction of or damage to these neurons may explain the finding that polio subjects were approximately twice as sensitive to experimentally-induced pain as were non-disabled controls (Figure 3)(53). It is hypothesized that increased pain sensitivity in polio survivors may be the result of decreased production of enkephalins by a reduced number of polio-damaged enkephalinergic neurons in both spinal cord and brain.

Increased pain sensitivity is reported clinically by polio survivors and must be acknowledged by clinicians when

administering therapies that are painful (e.g., stretching) and when treating acute pain. A number of patients have reported that they are not believed when describing their heightened sensitivity to pain, and have been refused adequate medication for acute (e.g., post-operative, post-traumatic) pain.

Conclusion

The ability of the polio virus to produce symptoms by its destruction of neurons outside of the anterior horn has been accepted for more than 100 years. It is only our recent experience with PPS that has forced us to recognize that both the people who survived the original viral onslaught and their central nervous systems have been operating for decades under extreme stress. This stress now may be combining with the aging of an extensively damaged but here-to-fore remarkably functional central nervous system to reveal the previously hidden symptoms of polioencephalitis.

The above-presented hypotheses concerning the etiology of PPS fatigue suggest that reductions in both emotional and physical stress will reduce PPS. This is the experience of post-polio clinics throughout the world (36,54,55,56). As PPS fatigue continues to be treated with stress-management, work simplification and energy conservation (see 36,56), the hypotheses are being tested by studying the neuroanatomy, neuroendocrinology and neuropsychology of PPS fatigue. In addition, pharmacological means for stimulating the RAS

that do not further metabolically stress its remaining aging, polio-damaged neurons are being tested.

REFERENCES

1 Barnhart M, Rhines R, McCarter, Magoun, HW: Distribution of lesions of the brain stem in poliomyelitis. Arch Neurol Psychiatry 1948; 59: 368-377. 2 Strumpell A: Ueber die acute encephalitis der kinder. Allg Wien med Ztg 1884; 29: 612.

3 Bodian D: Poliomyelitis: Neuropathologic observations in relation to motor symptoms. J Am Med Assoc 1947; 134: 1148-1154.

4 Bodian D: Histopathological basis of clinical findings in poliomyelitis. Am J Med 1949; 6: 563-578.

5 Howe HA, Bodian D: Neural Mechanisms of Poliomyelitis. New York, The Commonwealth Fund, 1942.

6 Guizetti HU: Betrachtungen zur poliomyelitis des hirnstammes. Deutsch Ztschr f Nervenh 1933; 131: 29-42.

7 Matzke HA, Baker AB: Poliomyelitis: A study of the midbrain. Arch Neurol Psychiatry 1951; 65: 1-15.

8 Peers JH: The pathology of convalescent poliomyelitis in man. Am J Pathol 1942; 19: 673-695.

9 Luhan JA: Epidemic poliomyelitis: Some pathological observations on human material. Arch Pathol 1946; 42: 245-260.

10 Bodian D: Poliomyelitis: Pathologic Anatomy, in Poliomyelitis. Philadelphia, Lippincott, 1949.

11 Snyder SH, and Childers SR: Opiate receptors and opioid peptides. Ann Rev Neurosci 1979; 2: 35-58.

12 Bodian D, Howe HA: Neurotropism and the genesis of cerebral lesions in poliomyelitis. Bull Johns Hopkins Hosp 1941; 68: 58-76.

13 Howe HA, Bodian D: Neuropathological evidence on the portal of entry problem in hman poliomyelitis. Bull Johns Hopkins Hosp 1941; 69: 183-214.

14 Bruno RL, Frick NM: Post-Polio Sequelae: Physiological and psychological poverview. Rehab Lit 1986; 47: 106-111.

15 Bodian D. Motorneuron disease and recovery in experimental poliomyelitis, in Hastead LS, Wiechers DO (eds): Late Effects of Poliomyelitis. Miami, Symposia Foundation, 1985.

16 Parsons PE: Data on polio survivors from the National Health Interview Survey. Washington, D.C., National Center for Health Statistics, 1989.

17 Bruno RL, Frick NM: Stress and "Type A" behavior as precipitants of Post-Polio Sequelae, in Halstead LS and Wiechers DO (eds): Research and Clinical Aspects of the Late Effects of Poliomyelitis. White Plains, March of Dimes, 1987.

18 Owen RR, Jones D: Polio redisuals clinic: Conditioning exercise program. Orthopedics 1985; 8: 882-883.

19 Buchanan AR: Functional Neuroanatomy. Philadelphia, Lea and Febiger, 1961.

20 Morruzi G, Magoun HW: Brain stem reticular formation and activation of the EEG. EEG Clin. Neurophysiol. 1949; 1: 455-473.

21 Daube JR, Reagan TJ, Sandok BA et al: An Approach to Anatomy, Pathology, and Physiology by Systems and Levels. Boston, Little, Brown, 1986.

22 Gelhorn E: Autonomic Imbalance and the Hypothalamus. Minneapolis, U. Minn. Press, 1957.

23 MacLean PD: Psychosomatic disease and the "visceral brain." Psychosom Med 1949; 11: 338-353.

24 Mesulam M-M: Attention, confusional states, and neglect, in Mesulam M-M (ed): Principles of Behavioral Neurology, Philadelphia, Davis, 1985.

25 Lou HC, Henriksen L, Bruhn P, et al: Striatal dysfunction in attention deficit and hyperkinetic disorder. Arch Neurol 1989; 46: 48-52.

26 Mandell AJ: Toward a psychobiology of transcendence, in Davidson JM, Davidson RJ (eds): The Psychobiology of Consciousness, New York, Plenum, 1980.

27 Pribram KH, McGuinness D: Arousal, activation and effort in the control of attention. Psych Rev 1975; 82: 116-149.

28 Bremer F: Cerveau isole et physiologie du sommeil. Comptes Rendus de la Societe de Biologie 1935; 118: 1235-1241.

29 Brown JR, Baker AB, McQuarrie, et al: Bulbar form of poliomyelitis. J Am Med Assoc 1947; 135: 425-428.

30 Meyer E: Psychological considerations in a group of children with poliomyelitis. J Pediatrics 1947; 31: 34-48.

31 Machado-Salas J, Scheibel ME, Scheibel AB. Neuronal changes in the aging mouse: Spinal cord and lower brain stem. Experimental Neurol 1977; 54: 504-512.

32 Mann DMA, Yates PO, Hawkes J: The pathology of the human locus ceruleus. Clinical Neuropathology 1983; 2: 1-7.

33 McGeer PL, McGeer EG, Suzuki JS: Aging and

extrapyramidal function. Arch Neurol 1977; 34: 33-35.

34 Vincent FM, Myers WG: Poliomyelitis and Parkinsonism. New Engl J Med 1978; 298: 1122. 35 Bruno RL: Predicting pain management program outcome: The Reinforcement Motivation Survey. Arch Phys Med Rehabil 1990; 10: 785 1990.

36 Bruno RL, Frick NM: The psychology of polio as prelude to Post-Polio Sequelae. Orthopedics 1991; (this issue).

37 Dewe PJ: Stressor frequency, tension, tiredness and coping. J Advanced Nursing 1989; 14: 308-320.

38 Hancock PA, Warm JS: A dynamic model of stress and sustained attention. Human Factors 1989; 31: 519-537.

39 Varney NR, Alexander B, MacIndoe JH: Reversible steroid dementia in patients without steroid psychosis. Am J Psychiatry 1984; 141: 369-372.

40 Henkin RI. Effects of ACTH, adrenocorticosteriods and thyroid hormone on sensory function, in Stumpf WE, Grant LD (eds): Anatomical Neuroendocrinology, Basel, Karger, 1975.

41 Born J, Kern W, Fehm-Wolfsdorf G, Fehm, HL: Cortisol effects on attentional processes in man as indicated by event-related potentials. Psychophysiology 1987; 24: 286-292.

42 Wolkowitz OM, Reus VI, Weingartner H, et al: Cognitive effects of corticosteriods. Am J Psychiatry 1990; 147: 1297-1303.

43 McEwen BS, De Kloet ER, Rostene W: Adrenal steroid receptors and actions in the nervous system. Physiological Rev 1986; 66: 1121-1188.

44 Reul JMHM, De Kloet ER: Anatomical resolution of two types of corticosterone receptor sites in rat brain with in vivo autoradiography and computerized image analysis. J Steroid Biochem 1986; 24: 269-272.

45 Reul JMHM, Sutanto W, van Eekelen JAM, et al: Central action of adrenal steroids during stress and adaptation, in Porter JC, Jezova D (eds): Circulating Regulatory Factors and Endocrine Function. New York, Plenum, 1990.

46 Phillips MI, Dafny N: Effect of a dose range of cortisol on brain unit activity. Fed Proc 1971; 30: 203.

47 Steiner FA, Ruf K, Akert K: Steroid-sensitive neurons in rat brain: Anatomical localization and responses to neurohumors and ACTH. Brain Res 1969; 12: 74-85.

48 Kadekaro M, Ito M, Gross PM: Local cerebral glucose utilization is increased in acutely adrenalectomized rats. Neuroendocrinol 1988; 47: 329-334.

49 Bodian D, Horstmann DM: Polioviruses, in Horsfall D

(ed): Viral and Rickettsial Infections of Man. Philadelphia, Lippincott, 1965.

50 Pezeshkpour GH, Dalakas MC: Long-term changes in the spinal cords of patients with old poliomyelitis. Arch Neurology 1988; 45: 505-508.

51 van Schijndel M, De Mey H, Naring G: Effects of behavioral control and Type A behavior on cardiovascular responses. Psychophysiology 1984; 21: 501-509.

52 Frankenhaeuser M: Psychobiological aspects of life stress, in Levine S, Ursin H (eds): Coping and Health. New York, Plenum, 1980. 53 Bruno RL, Johnson JC, Berman WS: Motor and sensory functioning with changing ambient temperature in post-polio subjects, in Hastead LS, Wiechers DO (eds): Late Effects of Poliomyelitis. Miami, Symposia Foundation, 1985.

54 Agre JC, Rodriquez AA, Sperling KB: Symptoms and clinical impressions of patients seen in post polio clinic. Arch Phys Med Rehabil 1988; 70: 367-370.

55 Peach PE, Olejnik S: Effects of treatment and noncompliance on Post-Polio Sequelae and muscle strength Orthopedics 1991; (this issue).

56 Young G: Energy conservatiion, occupational therapy and the treatment of Post-Polio Sequelae. Orthopedics 1991; (this issue).

57 Pare WP: The effect of chronic environmental stress on premature aging in the rat. J Gerontol 1965; 20: 78-84.

58 Rosenheimer JL: Effects of chronic stress and exercise on age-related changes in end-plate architecture. J Neurophysiol 1985; 53: 1582-1589. 59 Stumpf WE, Sar M: Steroid hormone target cells in the extrahypothalamic brain stem and cervical spinal cord. J Steroid Biochem 1979; 11: 801-807.

60 Dekosky ST, Scheff SW, Cotman CW: Elevated corticosterone levels: A possible cause of reduced axon sprouting in aged animals. Neuroendocrinol 1984; 38: 33-38.

61 Weichers DO: Acute and latent effect of poliomyelitis on the motor unit as revealed by electromyography. Orthopedics 1985; 8: 872-872.

Figure Legends

Figure 1. Brain areas lesioned by the polio virus as seen in 158 human autopsies. Severe lesions: Reticular formation (RF), vestibular nuclei (V), cerebellar roof nuclei (R), periaquiductal gray (PG). Moderate lesions: Posterior hypothalamic nuclei (P), paraventricular hypothalamic nucleus (PV), substantia nigra (SN). Mild lesions: Thalamic nuclei (T), preoptic hypothalamic nuclei (PO), locus ceruleus (LC), median raphe nuclei (MR).

Figure 2. Polio-virus lesions within the reticular activating

system (arrows): Thalamic nuclei (T), posterior hypothalamus (P), substantia nigra (S), reticular formation (RF), and locus ceruleus (LC).

Figure 3. Linear regression of subjective rating of stimulus intensity on applied stimulating current as a measure of pain sensitivity in post-polio and non-disabled control subjects (see 51).