SPINAL CORD INJURY

Edited by
N. Eric Naftchi

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FOREWORD

We shall not, and those who come after us must not, accept the goals that were not reached yesterday as unsurmountable today or tomorrow. We will strive to render the world of the paralyzed-on-wheels but a transitory stop, and settle for nothing short of optimal recovery.

N. Eric Naftchi

In man, the process of "encephalization" culminates in almost complete control of the brain over the lower centers. Transection of the spinal cord severs the extensions of its nerve fiber tracts running to and from various brain centers. Although there is some confusion on the meaning of spinal shock, it is supposed to last from two to three weeks or longer in man, compared with less than a few minutes in the frog. This is a testimony to the complexity of the suprasegmental control in higher animals. Since the brain exerts its control over the internal environment through several monoamine, amino acids, and peptide neurotransmitters, it should not be surprising if the metabolism of these transmitters is found to be drastically altered along with other physical and metabolic dysfunctions which ensue following the spinal cord section.

In spite of the major strides in rehabilitation of traumatic spinal cord injury, our knowledge of the etiology underlying the diverse neurophysiologic derangements remains limited. For instance, we are just becoming aware of some of the changes in the "milieu interieur." The constancy of this internal enviroment is ordinarily integrated between normal functioning of the central and autonomic nervous systems on the one hand, and the endocrine glands on the other. We still have much to learn about the fate of the biogenic amine, amino acid, and peptide neurotransmitters in the CNS after a spinal cord transection. Do their biosynthesis, metabolism, storage, release, and re-uptake mechanisms change? If so, how do these changes affect the hypothalamic-hypophyseal relationship, vasomotor, and temperature regulating centers. In turn, how do the foregoing alterations affect the functions of the endocrine glands, the target organs, and the circulatory system? What are the causes of stress intolerance, spasticity, calciuria, osteoporosis, trohpic skin ulcers, and so on?

This foreword, therefore, will serve as a cursory review of three major areas of dysfunction encountered in spinal-cord-injured humans. It will also suggest some future areas of research directed towards elucidation of the pathophysiology of spinal cord injury. Finally, this investigator suggests boldly that re-education and restoration of sensory-motor function should be our ultimate aim. It is in the realm of possibility and must be vigorously pursued.

A frequent and serious complication of spinal cord injury, occurring immediately after the onset of the lesion, is the loss of bone minerals and

bone matrix. This loss of bone (resorption) results from a concomitant loss of calcium and hydroxyproline. The latter is a major amino acid found in collagen which is the main component of the bone matrix. The progressive loss of bone leads to osteoporosis and a negative calcium balance.

In spinal cord injury, extremely rapid and progressive loss of bone is often associated with kidney stone formation, pathologic fractures, and the development of ectopic bone. The purposes of the studies on bone demineralization were to: determine when the process of loss begins, find the extent and duration of the loss, find the reason for the loss, and retard and/or prevent the loss.

The results of our work and those of other investigators have shown that hypercalciuria occurs in spinal cord injury during the first six months postinjury and that the calcium excretion becomes less severe thereafter presumably due to increased patient activity. A longitudinal investigation of the degree of calcium and hydroxyproline loss, measured at weekly intervals, in paraplegic and quadriplegic subjects was conducted. The data from our longitudinal study show that the increase in urinary calcium starts almost immediately after the onset of injury. The elevated urinary calcium cannot simply be attributed to prolonged inactivity since the degree of calciuria is greater in spinal-cord-injured persons than in normal control subjects following prolonged bed rest.

Total urinary hydroxyproline is used as a sensitive index and quantifier of bone collagen metabolism. An increase in urinary hydroxyproline following spinal cord injury indicated collagen breakdown and bone resorption. In our longitudinal studies, we found that the excretion of hydroxyproline was greater and of longer duration in quadriplegics than in paraplegics. The correlation between hydroxyproline and calcium excretion in spinal-cord-injured subjects, without concomitant marked increases in serum alkaline phosphatase, indicates that the loss of calcium and hydroxyproline is consistent with bone resorption.

Thyrocalcitonin usually counteracts parathormone to keep plasma and bone exchange of calcium at a constant level. This hormone's effect is produced by the inhibition of bone resorption, especially when bone resorption is stimulated by the parathyroid hormone. Parathyroid hormone is also known to increase urinary excretion of hydroxyproline. Possibly, the main effect of thyrocalcitonin in humans is to protect against excessive bone loss due to parathyroid hormone.

In our studies on animal models with spinal cord injury, administration of thyrocalcitonin to paraplegic rats resulted in a marked improvement of calcium, phosphorus, and magnesium balances that were depressed following spinal cord injury. Another significant finding was that after transection of the spinal cord at the T_5 level, the survival rate in thirty untreated male Wistar rats was 25 percent. Death usually occurred within eight to fourteen days after transection although the urinary bladder was expressed three times daily. Autopsy revealed hydronephrosis of the kidneys which occurred either bilaterally, or, more often, unilaterally on the right side. Thyrocalcitonin administered subcutaneously increased the survival rate to 80 percent and markedly reduced the indicence of hydronephrosis.

Another complication of spinal cord injury is heterotopic ossification (myositis ossificans, extraskeletal, ectopic, or periarticular bone) which occurs in 16 to 53 percent of spinal-cord-injured victims. This condition starts as an inflammatory reaction causing edema, chrondrogenesis, and osteogenesis. Its etiology may possibly be related to autonomic dysfunctions commencing with the appearance of venous thrombosis and arteriovenous shunts in the affected area. The intimate association of osteoporosis with

periarticular ossification indicates that excessive calcium loss from bones is one of the predisposing factors in the formation of ectopic bone. In a preliminary study, the effect of thyrocalcitonin on ectopic bone was studied in three subjects. One paraplegic subject with long duration periarticular ossification of both hips was treated for a month with thyrocalcitonin. The serum ionized calcium, which is the exchangeable calcium between bone and plasma, decreased significantly after thyrocalcitonin therapy while the total calcium did not change appreciably. The results of ^{18}F scintimetry revealed that, after one month of thyrocalcitonin treatment, the enormous uptake observed before treatment had diminished to insignificant amounts in the affected areas. Clinically the range of motion in the above paraplegic subject increased by 25 degrees (from -35 to -10) and localized pain was significantly decreased. These results were not duplicated in the two other paraplegic subjects with short duration heteroptopic ossification. The response to thyrocalcitonin therapy may be different in an immature periarticular bone compared with that of one almost grown to maturity. The maturity of the heterotopic ossification is also of great importance in surgical intervention as well; surgery performed too early results in the regrowth of the extraskeletal bone. Immature periarticular bone may require a larger dose of thyrocalcitonin.

Another pharmacologic agent, diphosphonate, administered in large doses, was found to block or retard the progressive soft tissue ossification in adults and children with myositis ossificans progressiva and prevented the recurrence of calcification after surgical removal of ectopic bone. Thyrocalcitonin and diphosphonate ameliorating effects on heterotopic ossification must be compared for efficacy as well as minimum side effects.

A further complication following spinal cord injury is the formation of renal calculi (kidney stones). Formation of kidney stones appears to be favored when the concentrations of sodium and potassium in the urine is decreased and that of calcium is increased.

Based on speculation that a low calcium diet may reduce hypercalciuria and prevent renal calculi and periarticular bone formation, the calcium intake of paraplegic and quadriplegic patients is often restricted. Findings of rapid bone mineral loss following spinal cord injury lead to the conclusion, however, that a low calcium diet may exacerbate bone resorption leading to the early development of osteoporosis.

In our recent study of the effect of a calcium diet, rats fed on high calcium diets had normal calcium balance following spinal cord transection as compared with a significantly depressed calcium balance in rats on normal calcium diets. Rats fed high calcium diets also retained more calcium than animals receiving the normal calcium ration. The testes and prostates in paraplegic rats fed a normal calcium diet were atrophied compared with the controls. No atrophy was observed in rats fed a high calcium diet. The data indicate that the occurrence of urinary tract infections was more prevalent and of longer duration in paraplegic rats fed a normal calcium diet than in those fed a high calcium diet. Furthermore, hydronephrosis occurred in several paraplegic rats fed the regular calcium diet but not in animals fed the high calcium diet. Examination of the kidneys and bladders in the transected rats fed a high calcium diet revealed no evidence of renal or bladder calculi.

Spinal cord injuries in the human male result in various degress of testicular atrophy and sterility in the majority of subjects and, in some cases, gynecomastia. The occurrence of mammary hypertrophy which is found occasionally in men with spinal cord injury may appear as early as three months or as late as five years after the onset of injury. Testicular atrophy is reported to occur in over 50 percent of human males. Metabolic and hormonal disturbances causing the impairment of fertility in spinal man

are not yet fully understood.

It is well known that in patients with spinal cord lesions above the sympathetic outflow, body heat regulation becomes extremely irregular due to the loss of sympathetic hypothalamic control of sweating and the skin blood flow regulation. There is no explanation as to why some patients with spinal cord injury develop stress intolerance, gynecomastia, testicular, atrophy, amenorrhea, etc., all manifestations of disturbed functioning of the endocrine system.

In our recent studies, concentrations of testosterone, luteinizing hormone (LH), and follicle stimulating hormone (FSH) in the serum of ten paraplegic and ten quadriplegic subjects were measured once a week for a period of four months from the onset of injury. In paraplegic subjects, serum FSH and testosterone levels were significantly lower than those of the age-matched normal controls for a period of two and six weeks after spinal cord injury, respectively. Following the above periods of time, serum concentrations of both hormones were not significantly different from those of the controls. In paraplegic subjects, serum LH concentrations were also within control levels. By contrast, in quadriplegic subjects, serum FSH was depressed for three weeks while testosterone and LH concentration remained significantly lower than those of the controls during the entire four month test period. Furthermore, in another group of ten chronic (one to six years after the onset of injury) paraplegic and ten chronic quadriplegic subjects, serum FSH concentrations were comparable to those of the normal controls. Although serum LH concentrations were at control levels in chronic paraplegic they were significantly depressed in chronic quadriplegic subjects.

Whether the depressed serum testosterone was due to a primary testicular deficiency or to a decreased secretion of LH from the pituitary gland causing less stimulation of testicular Leydig cells remains to be investigated. In addition, it is not known whether low serum LH levels are due to pituitary deficiency or to a low level of pituitary stimulation by the hypothalamic LH releasing hormone. The low concentrations of the latter hormone could result from altered feedback involved in the function of the hypothalamic-pituitary-gonadal axis which is permanently disturbed in the acute and chronic quadriplegic subjects.

The purpose of biochemically stressing subjects is to determine the extent of remaining function, (i.e., the ability to respond to different degrees of stress). In this study, we wished to compare the response of spinal-cord-injured subjects to insulin induced hypoglycemia with that of controls.

The response to insulin induced hypoglycemia in spinal cord injury showed that 30 minutes after insulin administration glucose decreased by 70 percent in the controls and paraplegics but only 40 percent in quadriplegic subjects. Correlating with glucose findings, plasma epinephrine levels increased fifteen fold in the controls, five fold in paraplegics, and were unchanged in quadriplegic subjects. The peak epinephrine release came after that of hypoglycemia at 45 minutes postinsulin administration.

The results indicate a dampening of physiological and reduced hypoglycemic response in quadriplegic subjects possibly due to lower demand for glucose utilization and/or insulin receptor subsensitivity as a result of the loss of supraspinal control and curtailment of sympathetic outflow.

Autonomic hyperreflexia, characterized by paraxysmal hypertension, has been well documented ever since Head and Riddoch and Guttmann and Whitteridge first described the symptoms in quadriplegia. Patients with high level spinal cord injury, above the sympathetic outflow, at the level of thoracic six vertebra (T_6), very often develop spontaneous hypertensive

crisis due to any one of several noxious stimuli. These stimuli usually arise from the urinary bladder because of cystitis or kidney stone formation or from the rectum because of constipation or rectal impaction. Since quadriplegic patients are generally hypotensive, the high pressures that develop represent pressure changes of a magnitude that can cause cerebrovascular accident and death of the subject.

Occurrence of paroxysmal hypertension and its associated and documented mortality in quadriplegic subjects during episodic autonomic dysreflexia is well known. We have shown that the severity of the attacks are comparable to the activity of serum dopamine-β-hydroxylase (DBH) and plasma norepinephrine concentration.

Dopamine-β-hydroxylase is the enzyme that synthesizes neurotransmitter norepinephrine from its precursor, dopamine. Evidence has been accumulated to show that both DBH and norepinephrine are released simultaneously from sympathetic nerve endings. The activity of both DBH in serum and norepinephrine in plasma are used as indicators of sympathetic activity.

The excretion of catecholamine (norepinephrine, dopamine, and epinephrine) metabolites in 52 randomly chosen subjects suffering from chronic spinal cord injury was significantly higher than that of 36 normal control subjects. Eighteen subjects with spinal cord injury were followed longitudinally for six months from the date of onset of injury. A long-term decrease in serum DBH activity occurred in quadriplegic subjects when compared with their initial level (just after the onset of injury). Another group of ten chronic quadriplegic subjects were kept as free as possible from conditions that would cause autonomic overactivity. Endogenous plasma norepinephrine levels in this group were also significantly lower than those of ten normal control subjects. The high excretion of catecholamine metabolites found in the first group of randomly selected spinal-cord-injured subjects, therefore, must be due to many subclinical, undetected episodes of autonomic dysreflexia.

Systemic arteriolar vasoconstriction during hypertensive crises in spinal man are due to "reflex" sympathetic activity in the distal cord stump, and the action of the postganglionic neurotransmitter, norepinephrine. We also established that the severe elevations of arterial pressure during this syndrome are associated with an unchanged cardiac output and a great increase in total peripheral resistance. Thus, the primary cardiovascular mechanism of the hypertensive episodes is systemic arteriolar vasoconstriction.

These findings provide the basis for the pharmacological treatment of the acute hypertensive crises and for maintaining normal blood pressures in those subjects who are chronically prone to repetitive, overt and/or subclinical hypertensive episodes. Aside from pheochromocytoma, this is the first time that a causative neurotransmitter has been unequivocably indentified in hypertension. Therefore, nitropruside or a short-acting ganglion blocker, trimethaphan camphorsulfonate, are most satisfactory for reducing arterial blood pressure during acute hypertensive episodes of autonomic dysreflexia. The use of antihypertensive medication such as long-acting ganglionic blocking agents, alpha adrenergic receptor blocking drugs and guanethidine, are potentially dangerous in quadriplegic patients because they can produce exaggerated postural hypotension and, therefore, may bring about catastrophic episodes of myocardial and cerebral ischemia.

In order to determine whether impaired sympathetic nerve response and/or impaired renin release are responsible for orthostatic hypotension in patients with cervical spinal cord lesions, serum dopamine-β-hydroxylase (DBH) activity and plasma renin activity (PRA) were examined during passive tilting in six quadriplegic patients and in six normal control

types and degrees of stresses.

The investigation will involve longitudinal, repetitive measurements of the effects of different levels of spinal cord lesion on (1) the concentrations of the catecholamines, serotonin, dopamine-β-hydroxylase activity, other peptide neurotransmitters, and Na^+, K^+, and Ca^{++} in the blood and cerebrospinal fluids, and the catecholamine and serotonin metabolites in the urine; (2) the reactivity of peripheral blood vessels to intravenously infused l-norepinephrine; (3) the uptake, release, and excretion of intravenously infused labelled-norepinephrine in spinal-cord-injured subjects and controls; (4) the cardiovascular, endocrinological, and biochemical responses to the stresses of head-up tilt, hypovolemia and insulin-induced hypoglycemia in spinal-cord-injured subjects and controls for each respective stress test.

The results from the above investigation and those in animal models will provide information about the disturbances in basic biological mechanisms caused by spinal cord injury and how they change after the onset of injury. This knowledge will permit more definitive estimation of the beneficial effects of currently used methods of rehabilitation, and the logical introduction of new pharmacological agents in this process. Thus, the conclusions from such investigations may hasten the rehabilitation of spinal-cord-injured subjects, make it more complete and, thus, prevent relapses and re-hospitalization.

The neuroendocrinological functional changes in paraplegic and quadriplegic subjects must be studied in depth. The major hormones such as ACTH, LH, FSH, TSH, vasopressin, cortisol, testosterone, thyroxine, etc. must be analyzed in the serum of spinal-cord-injured subjects by the most sensitive and specific methods available. These techniques include radioimmunoassay and high pressure liquid chromatography. Immunocytochemistry must be used for localization of hormones in tissues. Thus, changes in negative feedback due to the degree of loss of supraspinal control will be measured and correlated with the time after the onset of spinal cord injury. Furthermore, the adaptive mechanisms to physical (head-up tilting, hypovolemia) and biochemical (insulin-induced hypoglycemia) stresses, and the degree of their deficiencies in spinal-cord-injured subjects require elucidation.

Our preliminary results on hypothalamic corticotrophic releasing hormone (CRF) and vasopressin seem to suggest that they act synergistically in the release of ACTH and that, in subjects with high-level spinal cord injury, the diurnal rhythm may be curtailed. The data indicate that the interruption of the afferent stimuli to the brain after spinal cord injury affects the CNS control of ACTH secretion and thus the release of cortisol.

Even in persons with intact spinal cords, receiving drugs which reduce normal compensatory reflex sympathetic nervous system activity, a small degree of blood loss can cause severe hypotension and syncope when supine. Although this question has not been adequately studied in spinal-cord-injured subjects, it must be presumed that those with high lesions are inordinately sensitive to blood loss.

The investigations of the physical and biochemical stresses in spinal-cord-injured humans are essential in order to identify the basic deficiencies, excesses and conditions of supersensitivity and/or subsensitivity which would result from the loss of supraspinal control and disturbance in negative feedback systems after spinal cord injury.

The results from previous studies have delineated some of the derangements in the metabolism of biogenic amines, disruption of other neurotransmitters, and autonomic impairment of cardiovascular regulation

subjects. Serum DBH was measured by an isotopic enzymatic method and PRA by radioimmunoassay. Following head-up tilting, quadriplegic subjects demonstrated a prompt significant decrease in mean arterial pressure (MAP) and an increase in heart rate. Dopamine-β-hydroxylase activity and PRA increased significantly in 15 minutes following tilt. In normal subjects, although heart rate increased, mean arterial pressure was unchanged and DBH and PRA did not increase significantly during head-up tilt. The findings of increased DBH during tilt hypotension in quadriplegic subjects provide evidence that reflex sympathetic nerve stimulation persists despite cervical cord transection. Increased PRA may be attributed to decreased renal perfusion pressure and increased sympathetic stimulation during tilt hypotension. In another study, we found that responses of eight paraplegic subjects to head-up tilt were not significantly different from those of eight normal controls but glomerular filtration rate (GFR) and renal plasma flow (RPF) were significantly lower in nine quadriplegics in the supine position. During tilt, RPF decreased significantly, but the fall in GFR was not significant. In all three groups, the GFR during head-up tilt was similar, indicating that in spite of the great loss of supraspinal sympathetic control, quadriplegic subjects apparently equally constrict their afferent and efferent renal arterioles during orthostatic stress and thus prevent excessive fall of GFR. These data further suggest that orthostatic hypotension in quadriplegic patients cannot be attributed solely to the failure of the sympathetic nervous system or the renin-angiotensin system to respond to the stimulus of orthostasis (erect posture).

Investigations of dysfunction of the endocrine and autonomic nervous system, and mineral metabolism must be continued in order to explain and treat the causes of the various disorders discussed. The long-term goals of our investigation of dysfunction in mineral metabolism are (1) to develop and standardize a method which measures the extent of osteoporosis in spinal-cord-injured subjects by computerized tomography; (2) to determine longitudinally the degree of bone demineralization in patients with paralysis due to spinal cord lesion by use of computerized tomography as early as possible after the onset of spinal cord injury and once a month for three months thereafter; (3) to initiate the treatment of paraplegic and quadriplegic subjects with thyrocalcitonin and diphosphonates immediately after the onset of injury in order to determine which drug is more efficacious in preventing osteoporosis and other complications such as renal and bladder stone formation and development of periarticular bone with the least amount of side effects; (4) to investigate the effect of thyrocalcitonin and diphosphonate therapy on periarticular bone formation and to prevent its restrictive, debilitating effects, either by inhibiting the formation of extraskeletal bone, or once formed, causing its resorption or maturation by pharmacologic means; (5) to measure the effect of dietary calcium on the amelioration or exacerbation of complications associated with dysfunction of mineral metabolism in animal models of spinal cord injury. If these results demonstrate conclusively that a high calcium diet has ameliorating effects, the experiment must be extended to humans under strict dietary control.

The long-term aim of our research in autonomic nervous dysfunction has been to measure the effects of different levels of spinal cord injury on the metabolism of catecholamines in man and to correlate these changes with the associated degrees of impairment of neural, endocrinal and cardiovascular functions. That is, to delineate the autonomic function of the spinal cord and sympathetic nervous system below the transection. These studies should be of particular importance with reference to the ability of the spinal-cord-injured subjects to tolerate and adapt to different

in paraplegic and quadriplegic subjects. Similar investigations regarding the interrelationships between neural, neuroendocrinal, and cardiovascular mechanisms are necessary to provide the basic knowledge required for more adequate means of rehabiliating and re-educating spinal-cord-injured patients based on sound medical principles.

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