Effect of Spinal Cord Transection on Adrenocortical Function.* (27387)

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It has recently been reported that adrenal cortical function is impaired in patients with spinal cord transection above the fifth thoracic vertebra, whereas, in patients with lesions below this level, secretion of adrenal steroid hormones is normal(1). In rats with spinal cord transection, the anterior pituitary does not release ACTH in response to electrical stimuli applied below the level of interruption of nerve pathways. When electric shock is applied above the lesion, however, ACTH secretion is normal as shown by a decline in adrenal ascorbic acid concentration (2). Although these data suggest that there are alterations in anterior pituitary and adrenal cortical hormone secretion after transection of spinal cord, systematic evaluation of this problem has not been carried out. It was of interest, therefore, to determine effect of cord transection on secretion and metabolism of adrenocortical hormones in man. Our results demonstrate that adrenal cortical function is not impaired by interruption of the spinal cord.

Materials and methods. Adrenocortical hormone secretion of patients with spinal cord transection was evaluated by determining urinary and plasma 17-hydroxycorticosteroid levels during ordinary activity and after ACTH and comparing them with those of similarly treated, healthy, control subjects. On the first day, a 24-hour urine collection was started at 8:00 a.m. and a plasma sample obtained at 4:00 p.m. The next day, 80 units of zinc corticotrophin were administered at 8:00 a.m. and a second 24-hour urine collection was started. At 4:00 p.m. on the second afternoon, another plasma specimen was taken. Urine and plasma were frozen immediately after collection and kept at −20°C until steroid determinations were done. Urinary 17-hydroxycorticosteroids were assayed by Silber-Porter technic(3) and plasma steroids were measured by method of Eik-Nes (4).

Diurnal variation of adrenal cortical secretion was studied in patients with cord lesions and controls (laboratory and hospital personnel) by determining plasma 17-hydroxycorticoid levels at 8:00 a.m. and 4:00 p.m. of the same day.

Metabolism of cortisol in patients and healthy volunteers was studied by infusing 1 mg of the steroid/kg body weight during a 30-minute period which began at 10:00 a.m. Plasma was usually obtained 1, 2, 3 and 4 hours after completion of infusion and 17-hydroxycorticosteroid levels determined. In certain instances, however, the 3-hour sample was omitted. Endogenous adrenal steroid secretion was suppressed in all subjects by administering 1.5 mg dexamethasone the night before and 0.75 mg the morning of infusion. Half-life of infused cortisol was determined by plotting the regression curve from observed plasma levels.

In patients with spinal cord lesions, the level of transection was determined clinically by careful neurological and radiological examinations. In each instance, sensory and motor deficits determined the level at which the cord lesion was considered to be complete.

Results. Urinary 17-hydroxycorticosteroid excretion of 10 control subjects during a day of ordinary activity was compared with that of 6 patients with cord transection above T-5 and 5 patients with lesions below this level (Table I). In neither instance were mean values significantly different. The increased urinary steroid excretion of controls in response to ACTH was likewise compared with that of patients with transections above and below T-5 (Table I). The difference was not significant in either case. Plasma corticoid levels in control subjects before and after ACTH were also compared with those of patients with cord lesions above and below T-5. In both groups of patients with spinal cord

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TABLE I. Effect of ACTH on Urine and Plasma 17-Hydroxycorticosteriod Levels in Control Subjects and Patients with Spinal Cord Transection.
(Mean Values ± Standard Error of Mean)

	Plasma 17-hydroxycorticoid level* (γ/100 ml)		Urine 17-hydroxycorticoid excretion (mg/24 hr)	
	Before ACTH	After ACTH	Before ACTH	After ACTH
Control subjects (10)	9.6 ± 1.1	26.7 ± 2.6	7.9 ± 1.0	24.0 ± 2.2
Cord lesions above T-5 (6)	8.0 ± .79†	28.0 ± 2.5	8.7 ± 3.0	21.6 ± 4.5
Cord lesions below T-5 (5)	6.8 ± 1.0†	22.4 ± 4.0	7.7 ± 1.4	18.9 ± 3.1

* Plasma specimens obtained at 4:00 p.m.
† Difference from control significant, P = < 0.01.

lesions, plasma steroid concentrations before ACTH were significantly less than those of control subjects (Table I). Despite lower initial 17-hydroxycorticosteroid levels, patients with cord transections responded to ACTH with a 3-fold increase in plasma hormone concentration (Table I). There was no statistical difference between the plasma steroid response to ACTH of control subjects and in both groups of patients.

Studies of diurnal variation of adrenocortical hormone secretion revealed that at 8:00 a.m. and 4:00 p.m., plasma 17-hydroxycorticosteroid levels of control subjects and patients with cord lesions above T-5 were almost the same (Table II). Plasma steroid levels of the group with transection below T-5 were significantly higher than those of control subjects. The explanation for this finding is not apparent. It was observed, however, that the decline in steroid concentration which occurred between 8:00 a.m. and 4:00 p.m. in these latter patients was not statistically different from that which occurred in controls or patients with cord transections above T-5.

Metabolism of cortisol was studied in 11 control subjects and 8 patients with spinal cord transection. The mean half-life of cortisol in the control group was 1.97 ± 0.1 hours, a value which is identical with that obtained by Peterson(5). In patients with cord lesions, the mean half-life of infused steroids was slightly longer (2.27 ± 0.2 hours); however, the difference was not significant.

Discussion. The role of afferent nerve impulses in initiation of ACTH release and subsequent adrenal cortical secretion has not been defined. Hume studied the adrenal cortical response to surgical procedures in patients with complete cervical cord transection and found no rise in plasma corticosteroids when operations involved denervated areas (6). When ACTH was administered to these subjects, a considerable rise in plasma hydroxycorticoids occurred, thus, demonstrating intact adrenocortical function. In dogs with cervical cord section, Hume found that 17-hydroxycorticoid secretion was subnormal during the first 30 minutes following abdominal laparotomy but after 60 minutes hormone secretion was normal(6). It was concluded from these experiments that transmission of afferent nerve impulses to the brain was an important factor concerned with release of ACTH. Because of the delayed adrenocortical response to laparotomy in cord-sectioned dogs, it was suggested that another substance, formed in injured tissues

TABLE II. Diurnal Variation of Adrenal Steroid Secretion in Control Subjects and Patients with Spinal Cord Transection.
(Mean Values ± Standard Error of Mean)

	Plasma 17-hydroxycorticoid level (γ/100 ml)		Difference between 8:00 a.m. & 4:00 p.m. levels
	8:00 a.m.	4:00 p.m.	
Control subjects (22)	15.7 ± .8	7.8 ± .6	7.9
Cord lesions above T-5 (5)	15.6 ± 1.0	8.2 ± 1.3	7.4
Cord lesions below T-5 (4)	20.0 ± 1.9*	10.9 ± .8*	9.1

* Difference from control significant, P = <.05.

and transported to the brain *via* the blood, was also involved in ACTH release.

Redgate studied the effect of electrical stimulation on adrenal cortical secretion in rats with spinal cord transection by measuring changes in adrenal ascorbic acid(2). He found that ascorbic acid concentration was not altered following stimulation below the level of cord section while application of current in areas with intact nerve supply induced a decline in ascorbic acid. Redgate concluded that in order for sensory stimuli to induce secretion of ACTH and adrenocortical hormones, afferent nerve impulses must be transmitted through the spinal cord to the brain (2). Confirmation of these results was obtained by Egdahl who showed that trauma to the leg of experimental animals elicited an increase in adrenal steroid secretion only if nerve supply to the extremity was intact(7). In this investigation, there was no evidence to suggest that a factor which could stimulate ACTH release was formed in injured tissues and transported to the brain in blood.

Adrenal cortical function of patients with spinal cord transections at various levels has been assessed by Robinson(1) who found that patients with cord lesions below the fifth thoracic vertebra excreted normal amounts of 17-ketogenic steroids, but in patients with cord sections above T-5 there was reduced steroid excretion. In contrast, Osborn *et al.* recently reported that plasma and urinary adrenal steroid levels were normal in 3 patients with cervical cord transection who were studied before and after surgical procedures (8). Results of our study are in agreement with those of Osborn, in that we observed normal urinary 17-hydroxycorticosteroid levels in cord-transected patients before ACTH, and a rise in hormone excretion in response to ACTH that was equal to that of controls. In addition, the increase in plasma steroid concentration after ACTH in cord-sectioned patients was as great as that which occurred in control subjects even though initial levels were somewhat reduced. Our investigation has also demonstrated that the diurnal variation of adrenal steroid secretion is not altered in patients with spinal cord transection, and thus provides further evidence that adrenal cortical function is not impaired by cord section, regardless of the level. The findings that urinary 17-hydroxycorticosteroid excretion was normal before ACTH and that both plasma and urinary steroid levels increased greatly after ACTH indicated that there was no abnormality in metabolic inactivation of adrenal cortical hormones in cord transected patients. That this was correct was shown when the disappearance of infused cortisol from plasma was determined in patients and control subjects, since the rate of steroid degradation in the 2 groups was almost the same.

These results demonstrate that spinal cord transection does not reduce secretory capacity of the adrenal cortex nor affect inactivation of corticosteroid hormones. It is clear, therefore, that failure of adrenocortical secretion to occur in cord-transected patients or animals when stimuli are applied below the level of cord section(2,6) cannot be attributed to impaired adrenal function. Instead, there is failure of ACTH release by the pituitary, probably because afferent nerve impulses do not ascend to the center which elaborates corticotrophin releasing factor. It is also possible that anterior pituitary function may be affected by cord section

Summary. Adrenocortical hormone secretion of patients with spinal cord transection has been studied by determining urinary and plasma 17-hydroxycorticosteroid concentrations before and after ACTH and by measuring diurnal variation in plasma adrenal steroid levels. These values were compared with those obtained from control subjects and no difference in adrenal hormone secretion was evident. Metabolic inactivation of cortisol was determined by infusing the steroid intravenously and measuring rate of disappearance from plasma. The rate of steroid degradation in cord-sectioned patients was not different from that of controls.

1. Robinson, R., Munro, A. F., *Nature,* 1958, v182, 805.

2. Redgate, E. S., PROC. SOC. EXP. BIOL. AND MED., 1960, v105, 528.

3. Silber, R. H., Porter, C. C., *J. Biol. Chem.,* 1954, v210, 923.

4. Eik-Nes, K., *J. Clin. Endo. and Metab.*, 1957, v17, 502.

5. Peterson, R. E., Wyngaarden, J. B., Serafim, L. G., Brodie, B. B., Bunim, J. S., *J. Clin. Invest.*, 1955, v34, 1779.

6. Hume, D. M., *Pathophysiologia Diencephalica* (Curri, S. B., Martini, L., Eds., Springer-Verlag, Vienna, Austria, 1958).

7. Egdahl, R. H., *Surgery*, 1959, v46, 9.

8. Osborn, W., Schoenberg, H. W., Murphy, J. J., Erdman, W. S., Young, D., *Surgical Forum*, 1961, v12, 485.

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Thyroid Iodine Metabolism in the Alloxanized Rat.* (27388)

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The influence of thyroid status on the metabolism of carbohydrates in diabetes has been extensively studied(1). The effect of diabetes on thyroid metabolism, on the other hand, has received relatively little attention. The few studies which have been conducted in this area have been limited to the histochemical or cytological approach(2,3). The study reported here was designed to explore the thyroidal metabolism of iodine in the alloxan-diabetic rat using I^{131} as a metabolic tracer.

Experimental. Male Sprague-Dawley rats (135 ± 5 g) were maintained on a diet with a controlled iodine intake (0.0012 g of iodine/kg of diet) or on Nutrena dog pellets. Test groups received 4 intraperitoneal injections of alloxan monohydrate (15 mg, 20 mg, 20 mg, 20 mg) spaced at 3-day intervals. Control rats received intraperitoneal water (1 ml). Test and control rats were fasted 12 hours prior to each injection.

One test group received subcutaneous Lente insulin after the third alloxan injection at a dose rate of 3 units/day. Prior to I^{131} studies (16th day) this was increased to 3 units/12 hours.

Blood glucose values were checked after the final alloxan injection and at the end of experiment. Elevated blood glucose values, polydypsia and polyuria were considered to indicate that a diabetic state had been induced and maintained.

Three days after the final alloxan injection (16th day) all rats received 30 μc of carrier free Na I^{131} by intraperitoneal injection. The first measurements of thyroid I^{131} uptake were made 24 hours after injection of the radioactive tracer. Successive measurements of the thyroidal I^{131} content were made every 24 hours until the experiment was terminated.

Thyroid I^{131} uptake measurements were carried out using the procedure of Wolff(4) with the following minor modifications. Rats to be counted were not anesthetized but were immobilized by wrapping them in a light plastic cover and mounting them in a restraining cage designed to permit a constant geometry between the areas to be counted and the shielded, directional crystal-scintillation counter (Nuclear Chicago). The distance between the sensitive volume of the crystal and the areas to be counted was set at 2 inches to minimize minor variations in the position of the rats. Corrections for isotope decay and background were made in the normal manner. Correction for I^{131} content in nonthyroidal tissues was made using the epigastric procedure of Wolff(4).

The percentage of injected I^{131} which was concentrated by the thyroid gland in 24 hours in a given animal was approximated by comparing the 24-hour count to the count obtained from a 30 μc I^{131} standard mounted in a thin walled plastic tube and held above the scintillation counter in the approximate position of the rat thyroid. This standard, prepared on the day of I^{131} injection, was counted at the same time as the thyroid glands

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