Plasma Cortisol Levels after Head Injury

LIONEL R. KING, M.D., ROBERT L. MCLAURIN, M.D.,
H. PAUL LEWIS, M.D., HARVEY C. KNOWLES, JR., M.D.

From the Divisions of Neurosurgery and Metabolism, University of Cincinnati, College of Medicine, Cincinnati, Ohio 45229

PHYSICAL stress, either surgical or traumatic, provokes an increase in the level of plasma cortisol which can be attributed to increased secretion rate rather than delayed removal.[2, 5, 16, 19] To our knowledge, studies of circadian variation of plasma cortisol levels following head injury have not been reported. In the healthy person during normal life activity the concentration of plasma cortisol is high in the morning, decreases during the day, and rises again during the night.[20] This diurnal rhythm is abolished in long-term unconscious patients and in those with disturbed sleep cycles.[4, 18, 20] Also, patients with central nervous system disease who are conscious but have lesions in the temporal lobe, or the pretectal or hypothalamic area demonstrate abnormal rhythms.[9] For these reasons the present study was designed to examine the effect of head injury upon cortisol secretion cycles as evidenced by changes in plasma levels of cortisol.

Methods

Observations were made on two groups of patients.

Control Group. This group consisted of five patients, 19 to 55 years of age, who were scheduled for elective lumbar or cervical laminectomy (Table 1). None had any known associated medical or surgical diseases. Venous blood samples were drawn at 4-hourly intervals during the 24-hour period before operation and for 24 hours and longer during and after operation. In the preoperative day the patients were designated as a "normal control" group. On the day of operation they were designated as a "surgery control" group. The patients received secobarbital sodium or pentobarbital during the evening before operation. Pre-anesthetic medication was meperidine, promethazine and atropine, and anesthesia was a combination of sodium pentothal, fluothane, nitrous oxide and oxygen. Anectine was used as a muscle relaxant when needed. Operation was started about mid-morning and completed in the early afternoon and lasted 2½ to 4 hours except in patient J. B. (8 hours). All patients were conscious by 5:00 p.m. on the day of operation.

Trauma Group. This group consisted of 13 patients, age 18 to 37 years, with various types of head injury (Table 2) and is designated as the "trauma" group. None had any chronic disease or major associated injuries. Venous blood samples were drawn at 4-hourly intervals throughout a period 36 hours beginning on admission to the Neurosurgical Service. This cycle of sampling was repeated in five of the patients three to five days post-injury and again at a more remote time post-injury depending on the state of the patient.

The neurological status of the trauma patients was assessed at the three periods of observation. The patients were divided into three sub-groups representing degrees of severity of injury based on the duration

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TABLE 1. *Patients Undergoing Elective Spinal Surgery. Control Group*

Patient	Age	Sex	Operation	Duration of Operation	Pre-Anesthetic Medication	Anesthesia
J. L.	44	F	Lumbar laminectomy and disc	4 hr., 11:45 a.m.–3:45 p.m.	Meperidine hydrochloride, 75 mg., 10 a.m.	Sodium thiopental, 500 mg., 11 a.m. Nitrous oxide, Halothane
D. B.	53	M	Lumbar hemilaminectomy L4, L5	2 hr. 40 min., 10:10 a.m.–12:50 p.m.	Meperidine hydrochloride, 75 mg., 8:25 a.m.	Sodium thiopental, 500 mg. / Succinylcholine chloride, 60 mg. / Methoxyflurane 1% } 9:35 a.m. 2 l. nitrous oxide + 1 l. oxygen + Methoxyflurane
W. C.	55	M	Lumbar laminectomy	2 hrs., 12:15–2:15 p.m.	Meperidine hydrochloride, 75 mg. / Sodium pentobarbital, 100 mg. / Promethazine hydrochloride, 25 mg., 10:40 p.m.	Thiamylal sodium, 250 mg. / Succinylcholine chloride, 60 mg. } 11:45 a.m. Halothane, 1%, Nitrous oxide, Oxygen
R. D.	36	M	Cervical laminectomy	2½ hr., 8:30–11:00 a.m.	Meperidine hydrochloride, 75 mg. / Sodium pentobarbital, 100 mg. / Promethazine hydrochloride, 50 mg., 6:45 a.m.	Sodium thiopental, 375 mg., 7:35 a.m. Meperidine hydrochloride, 25 mg., 9:45 and 10:15 a.m. Flaxedil triethiodide, 80 mg., 7:40 a.m. Halothane, Nitrous oxide
J. B.	19	M	Neurofibroma bone cyst of 3rd lumbar root	8 hr. 14 min., 8:13 a.m.–4:27 p.m.	Meperidine hydrochloride, 75 mg. / Sodium pentobarbital, 50 mg. / Promethazine hydrochloride, 25 mg., 7:00 a.m.	Sodium thiopental, 240 mg. / Succinylcholine chloride, 60 mg. } 7:25 a.m. Halothane, Nitrous oxide, Oxygen

of unconsciousness and neurological abnormalities on admission to the hospital (Table 3).

Plasma cortisol was determined fluorimetrically by the method of Mattingly.[13]

In the control group, regression curves of plasma cortisol over time were calculated for 12-hour periods for the day before and the day of operation. In the trauma group, curves were calculated for the 20-hour period starting at the time of admission. Comparisons of slopes and mean elevations of the curves were made by covariance analysis (Snedecor).[22]

Results

Control Groups. The plasma cortisol values in the "normal" and "surgery" control groups are given in Table 4 and shown in Figure 1. The mean level at 8 a.m. on the preoperative day was 18.0 mcg./100 ml., decreased to 5.0 mcg./100 ml. at 8 p.m., and rose to 13.4 mcg./100 ml. at 8 a.m. on the day of operation. The mean levels of the two-12 hour whole periods were 12.0 and 8.5 mcg./100 ml., respectively, and were not significantly different. However, the slopes of the two regressions were -0.97 and $+0.79$, respectively, and were significantly different ($p < 0.01$). The findings are those of normal diurnal rhythm of plasma cortisol levels.[20]

In contrast, on the day of operation the mean cortisol level increased from 13.4 mcg./100 ml. at 8 a.m. to 29.6 at 8 p.m. The slope, $+1.30$, was significantly different from that of -0.97 of the same period of the preoperative day ($p < 0.01$), and the 12-hour mean level of 22.1 mcg./100 ml. was above that of 12.0 of the same

TABLE 2. *Patients with Cranial Trauma. Trauma Groups According to Degree of Injury*

Patient	Age	Sex	Diagnosis	Area of Injury and Duration of Coma	Approximate Time of Injury	Time First Blood Drawn Post-Injury
Group I						
W. L. 463807	37	M	Cerebral contusion, skull fx., mult. contusion and lacerations	Concussion—12 hr.	1:39 a.m.	11½ hr.
J. K. 463833	34	M	Cerebral contusion, basilar skull fx., occipital laceration, poss. renal contusion	Concussion—12 hr.	3:57 p.m.	8 hr.
R. S. 463803	25	M	Cerebral contusion	Concussion—6 hr.	11:30 p.m.	½ hr.
H. W. 463767	28	M	Cerebral contusion, fx. mandible, post-dislocated hip, Fx. L patella, lacerations	Left frontal lobe—24 hr.	6:01 a.m.	2 hr.
Group II						
J. P. 463875	30	M	Chronic subdural hematoma LF, infarction parietal lobe LP	Left frontoparietal—9 days	11:00 p.m.	36 hr.
J. R. 463718	18	M	Cerebral contusion, basilar skull fx.	Brain stem—48 hr.	Between Mid. and 2 a.m.	12 hr.
M. S. 467411	22	M	Cerebral contusion, small intracerebral hematoma	Right frontal—left occipital—basal ganglia—4 days-died	3:43 a.m.	9 hr.
R. A. 463854	32	M	Cerebral contusion, extensive sk. fx. L frontal orbital area, and R temporo-parietal region	Left hemisphere—24 days	5:50 p.m.	3 hr.
Group III						
S. G. 464146	18	F	Acute subdural hematoma L	Left hemisphere contusion—5 days—died	12:18 a.m.	12 hr.
D. G. 466786	23	M	Brain stem contusion, cerebral contusion	Brain stem—25 days	Between 10 p.m. and Mid	9 hr.
J. M. 322405	24	M	Cerebral contusion	Right hemisphere—6 hr.	8:59 p.m.	20 hr.
P. T. 470073	19	F	Cerebral contusion	Right hemisphere—11 days	7:48 p.m.	½ hr.
M. W. 355737	19	M	Brain stem contusion	Right hemisphere Brain stem—4 mo.	1:45 a.m.	7 hr.

TABLE 3. *Grading of Degree of Injury in Trauma Group*

Grade	Duration of Unconsciousness	Grading Grade	Neurologic Deficit
1	2 hr. or less	1	No specific deficit
2	2 to 24 hr.	2	Transient deficit (<12 hr.)
3	24 hr. to 4 days	3	Persistent deficit
4	Longer than 4 days	4	Decerebrate longer than 12 hr.

The sum of grades determines group assignment

Sum of Grades		Group
2 or 3	=	I
4, 5 or 6	=	II
7 or 8	=	III

period of the preoperative day ($p < 0.01$). In the second 12-hour period the mean value of 26.8 mcg./100 ml. also exceeded that of 8.5 of the same period of the preoperative day ($p < 0.01$). The slope of this regression, −0.38, was not significantly different from zero and did not differ from that of +0.79 of the same period of the preoperative day. In essence, operation caused both disruption of the normal diurnal rhythm and elevation of the mean levels.

Trauma Group. The plasma cortisol levels in the trauma patients determined at 4-hour intervals for periods up to 36 hours after admission are given in Table 5 and shown in Figure 2 according to degree of trauma. The values obtained in the first 20 hours were used to calculate regression curves. The mean initial levels were 39 mcg./100 ml. for sub-Group I, 51 for sub-Group II, and 47 for sub-Group III. The means for the whole 20-hour periods of the three sub-Groups were 35.0, 48.7, and 45.4 mcg./100 ml., respectively. All mean levels were significantly above those observed in the surgical control group ($p < 0.01$). The mean level of 48.7 mcg./100 ml. of sub-Group II was above that of sub-Group I ($p < 0.01$), but there was no significant difference between the mean values of sub-Groups III and I.

When the data of the three trauma groups were pooled, the common regression slope was −0.64 and in comparison with a line of zero slope was significant

TABLE 4. *Plasma Cortisol Levels (μg/100 ml) in Control Groups before and During Elective Vertebral Surgery. Regressions of 12-Hour Periods with Mean Levels ($\bar{Y}$) and Slopes (b) of Periods*

Subject	Presurgery						Surgery								
	8 a.m.	12	4	8 p.m.	12	4	8 a.m.	12	4	8 p.m.	12	4	8 a.m.	12	4 p.m.
J. L.	19	6	4	3	5	8	16	6	24	25	21	34	35	17	6
W. C.	18	14	20	9	8	17	16	8	10	45	31	22	21	18	
J. B.	21	17	29	6	2	16	12	35	27	49	36	41	31	36	18
R. D.	21	17	3	2	6	1	9	28	34	23	35	11	20	25	
D. B.	11	8	7	5	2	13	14	29	28	6	15	15	21	22	
Mean	18	12	13	5	5	11	13	21	25	30	28	25	26	24	
Regression	$\hat{Y} = 25.6 - 0.97X$			$\hat{Y} = -2.6 + 0.79X$			$\hat{Y} = -0.4 + 1.3X$			$\hat{Y} = 30.1 - 0.38X$					
$\bar{Y}$	12.0			8.5			22.1			26.8					
b	−0.97			+0.79			+1.3			−0.38					

TABLE 5. *Plasma Cortisol Levels (μg/100 ml.) in Trauma Patients after Admission. Progressions of 20-Hour Periods with Mean Levels ($\bar{Y}$) and Slopes (b)*

Subgroup	Patient	Hours After Admission									
		0	4	8	12	16	20	24	28	32	36
I	J. K.	48	57	50	36	34	38				
	W. L.	41	27	24	16	13	20				
	R. S.	5	10	21	25	26	27	$\hat{Y}^1 = 50.5 - 0.86\,X$			
	H. W.	62	84	72	46	31	28	$\bar{Y} = 35.0$			
		—	—	—	—	—	—				
	Mean	39	44	42	31	26	28	$b = -0.86$			
II	J. P.	48	41	37	37	27	33	30	31	33	27
	R. A.	31	46	61	62	55	57				
	J. R.	55	48	51	36	44	35	$\hat{Y}^1 = 55 - 0.35\,X$			
	M. S.	70	77	49	56	48	64	$\bar{Y} = 48.7$			
		—	—	—	—	—	—				
	Mean	51	53	50	48	44	47	$b = -0.35$			
III	S. G.	41	38	44	33	39	33				
	D. G.	57	77	91	91	59	52				
	J. M.	31	26	22	22	31	23				
	P. T.	74	80	68	59	44	48	$\hat{Y}^1 = 57.8 - 0.69\,X$			
	M. W.	31	39	31	33	22	24	$\bar{Y} = 45.4$			
		—	—	—	—	—	—				
	Mean	47	52	51	48	39	36	$b = -0.69$			

[1] Zero hour of regressions adjusted to 8 hours for comparison of slopes with control group.

at the 0.05 level of probability, indicating a gradual decrease of cortisol concentration with time. The scatter of values was considerable, however, and in most instances the levels increased in the first hours after admission. Thus, the levels demonstrated no diurnal rhythm as well as being markedly elevated. A firm relation between estimated degree of neurologic injury and elevation of plasma cortisol was not evident although those with milder injury had lower levels.

Three complete studies were done in each of the five patients with head injuries (one in sub-Group II, four in sub-Group III), and the data are given in Table 6. Patients J. M. and J. R. were restudied five days post-injury and eleven or twelve days post-injury (Fig. 3a-b). At five days post-injury the levels were not unusually elevated but tended to be higher than in the later study. In addition, while there was a suggestion of a circadian cycle at five days post-injury, this was not as definite as in the later study. Both patients had cerebral contusions, were unconscious for three days (J. R.) and eight days (J. M.), but had recovered thereafter without any localized neurological residuum clinically. Both returned to their original employment and remain well.

Patient P. T. with cerebral contusion did not regain consciousness until twelve days post-injury. By the third study she had been home for ten days, but was still unsteady and had mild spasticity and hemiparesis. She was oriented, alert, and able to care for herself. The first two studies are similar except for the higher levels on the day of injury (Fig. 3c). The study at one month post-injury is within the range of normal both for height of level and for circadian pattern.

Patients D. G. and M. W. had brain stem contusions, remained unconscious for several weeks and had neurological residuals. D. G., on repeated studies, had more normal levels, but no normal circadian pattern

TABLE 6. *Plasma Cortisol Levels (μg/100 ml.) in Trauma Patients. Levels Determined at Time of Injury and Later*

Patient	Time of Study	Hour					
		0	4	8	12	16	20
J. M.	Admission	31	26	22	22	31	23
	5 days	16	14	17	13	20	15
	11 days	11	8	4	8	19	10
J. R.	Admission	55	48	51	36	44	35
	5 days	16	12	8	11	18	22
	12 days	16	14	8	7		23
P. T.	Admission	74	80	68	59	44	48
	3 days	28	31	33	57	46	48
	1 mo.	29	11	11	11	5	10
D. G.	Admission	57	77	91	91	59	52
	5 days	21	22	19	22		23
	4 mo.	25	7	16	20	22	27
M. W.	Admission	31	39	31	33	22	24
	6 days	16	24	23	34	26	21
	4 mo.	35	21	20	20	18	39

(Fig. 3d). By four months post-injury he was conscious but had an erratic sleep-wake cycle and was under stress from urinary tract and pulmonary infections. He remained dysphasic and spastic, could not walk, nor take care of himself in any way, but would eat when fed. M. W. had no change in any of his studies (Fig. 3e). At the time of the last study, four months post-injury, he was generally spastic with marked clonus and few spontaneous movements. He was unconscious and required complete care, including tracheostomy.

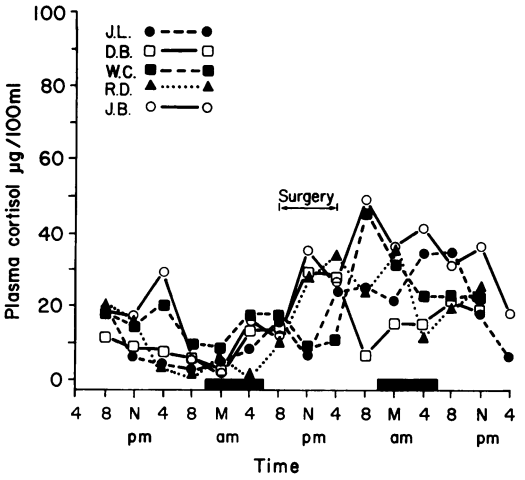

FIG. 1. Plasma cortisol levels at 4-hour intervals in elective surgery. Sampling started 24 hours before surgery and continued for at least 24 hours after patient had regained consciousness.

Discussion

Elevated plasma cortisol levels post-trauma reflect elevated ACTH levels, although these may be elevated intermittently rather than continuously.[19] The head injury patients in this study had plasma cortisol levels that were higher and remained elevated longer than the patients who had elective operations. This would imply that the increased ACTH secretion rates persist longer due to continued stress, or else are of the same short duration but are higher. The "dose-response curve" for ACTH-cortisol is such that maximum adrenal steroid output (plasma cortisol levels of 40–70 micrograms/100 ml.) is stimu-

lated by plasma ACTH levels at approximately 5 microunits/100 ml. Higher ACTH levels stimulate the same maximum cortisol secretion rate but it is prolonged in time.[6, 12] This continuous high level of adrenal secretion may contribute to the severe catabolic response with marked tissue wasting seen in head injury patients.

The height of the plasma cortisol level correlated poorly with the clinical estimate of degree of trauma. This may relate to difficulty in clinical assessment of degree of trauma in injured patients, or else a true disparity between clinical severity and metabolic severity. The patients with severe trauma who had abnormally elevated levels as late as four months post-injury had other forms of stress not related to cerebral function which may have contributed to these elevations. Because of differing sensitivity of the hypothalamic-pituitary-adrenal axis at different times of the day,[10] we attempted to correlate time of injury with height of level but did not have sufficient distribution of cases to draw conclusion on this point.

Pathways mediating ACTH response to systemic trauma have been well defined by Hume and Egdahl.[7] Stimuli from the injured area traverse the peripheral nerves, ascend through the spinal cord and brain stem to integrating centers in the reticular formation and limbic areas, where these impulses may or may not be modified by stimuli descending from the cerebral cortex. Impulses are then transmitted to the median eminence where corticotrophin releasing factor is liberated. This travels to the anterior pituitary through the hypothalamic-hypophyseal portal vessels and in turn releases ACTH which is then transmitted via the systemic circulation to the adrenal gland and stimulates secretion of cortisol.

When the brain itself is injured, the

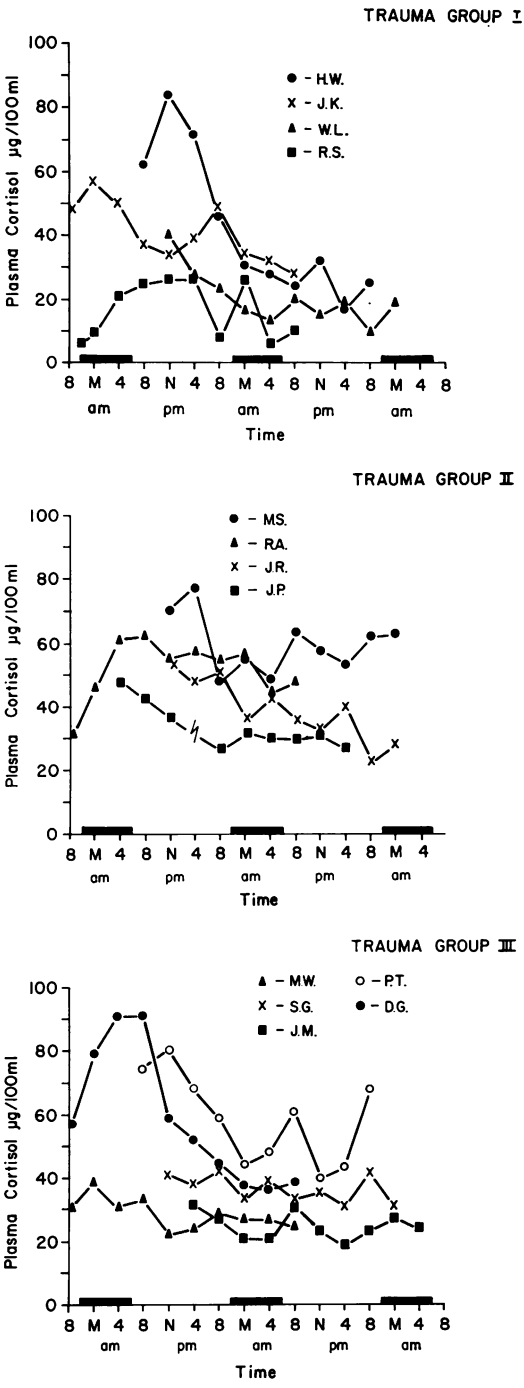

FIG. 2. Plasma cortisol levels at 4-hour intervals in head injury patients for 36 hours after admission to the hospital. The patients are grouped according to severity of trauma.

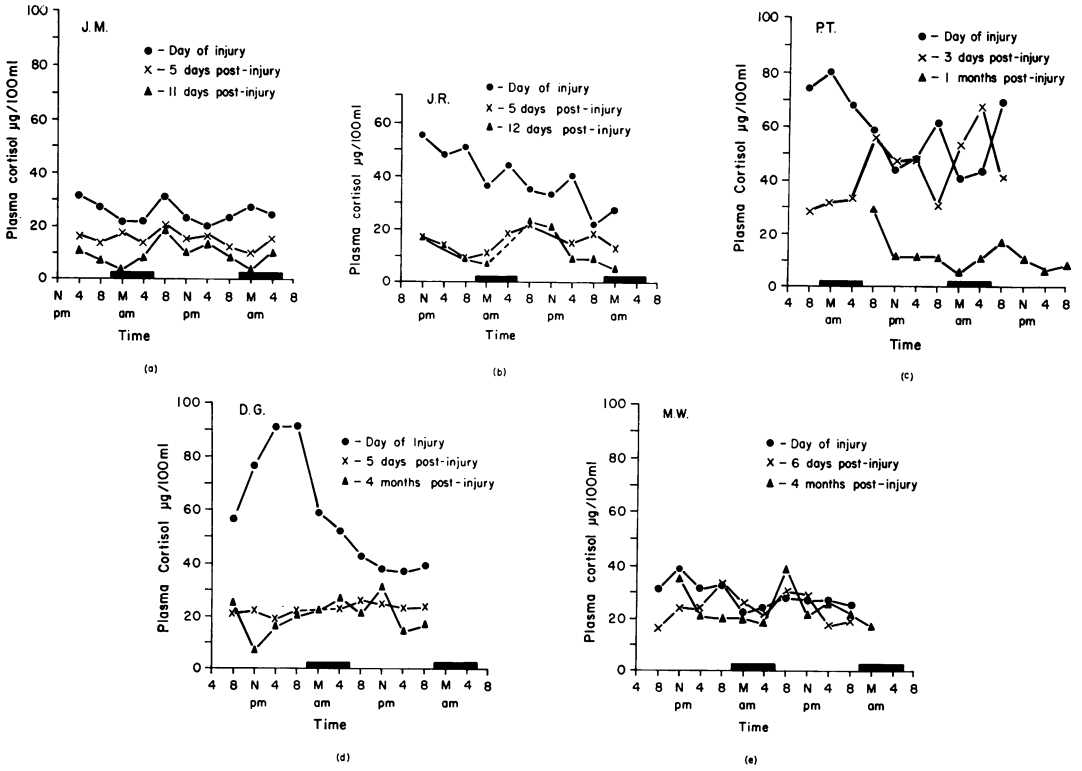

FIG. 3. Plasma cortisol levels at 4-hour intervals in 36-hour cycles repeated at various times post-injury. J. R. is in Trauma Group II; the others are in Trauma Group III. For diagnosis and duration of coma in each patient see Table 2.

pathways are not as explicit. ACTH secretion may be affected directly by a) stimulation of cortical or subcortical areas which themselves may be exerting a stimulating or inhibiting influence on the hypothalamus, b) sever communications between the hypothalamus and other areas by inactivating the integrating centers, or c) stimulate, inhibit, or destroy hypothalamic or pituitary centers directly.

Under normal circumstances ACTH release is regulated by stress (either psychological or physical), plasma level of cortisol (negative feedback), and circadian periodicity.[3] These regulatory phenomena are dependent on the integrity of the hypothalamic-pituitary axis but may be subserved by different areas and different pathways within the axis. In normal subjects the circadian pattern is affected readily by changes in the sleep-wake cycle which may have been a factor in patient D. G. Continued unconsciousness probably is the explanation in patient M. W. The mildly injured patients (Group I) were conscious during most of the study but still demonstrated no recognizable circadian pattern. This may have been due to continuing disruption of integrating centers in the reticular formation whose function was returning more slowly. On the other hand stress itself may desynchronize the pattern or totally obscure it because of abnormally elevated plasma levels. The postoperative patients did not have re-establishment of the pattern during the first 24 hours after recovering from anesthesia.

Dissociation between these regulatory phenomena have been well documented in patients with lesions in the hypothalamic

region. Loss of feedback responsiveness has been demonstrated in the face of adequate response to stress either artificially induced, i.e., pyrogen injection or insulin injection, or naturally occurring, i.e., surgical manipulation.[1, 8, 11] Other patients have exhibited adequate releasing mechanism but lack of suppression of ACTH release by high levels of plasma cortisol.[15, 17] Loss of circadian pattern, however, seems to be the most sensitive indicator of disruptive lesions in this area. Perhaps, as suggested by Krieger, phenomena which involve regulatory processes extending over a 24-hour period may be more sensitive to minor disruptions of hypothalamic pathways than transient stress-induced responses.[11] In addition, the pathways influencing circadian periodicity because of their diffuse representation may be disrupted without a specific hypothalamic lesion being present.

Considering the great prevalence of head injury, the incidence of clinically evident hypopituitarism as a sequelae is exceedingly rare. In testing a series of head-injured patients who did not present clinical evidence of endocrine dysfunction or abnormal basal excretion of urinary 17-hydroxycorticosteroids, about one third demonstrated "limited ACTH reserve" as measured by response to metyrapone.[21] The only clinical fact that could be gleaned from this group was that those with "limited ACTH reserve" had been unconscious for a longer time than those who gave a normal response to metyrapone. This would suggest minor damage to or disruption of the regulatory function of the reticular formation. McCarthy, in a smaller number of cases, found approximately the same incidence (4/11) of "limited ACTH reserve" in post-head injury patients who were tested with metyrapone.[14] These four also had been unconscious for longer periods of time than those who responded normally. Three of the four showed poor suppression with dexamethasone, indicating that in reality the patients had adequate synthesis and release of ACTH but some of the finer points in regulation of this release were at fault. Circadian pattern of plasma cortisol was not measured in these patients.

The head-injured patient, though apparently normal both neurologically and endocrinologically to the usual clinical examination, may in reality still be suffering from inability to monitor and regulate the more subtle aspects of his day-to-day living.

Summary

Observations were made of plasma cortisol levels in 13 patients with cranial trauma. Values obtained pre- and postoperatively from five normal subjects undergoing elective spinal operations were used as controls. Determinations were made at four-hour intervals in control and trauma groups. The trauma patients were subgrouped according to degree of trauma.

The control group demonstrated normal levels with normal circadian rhythm on the preoperative day. On the day of operation the levels were significantly elevated and the rhythm disrupted. In trauma patients levels were significantly higher than in the surgical patients and also without discernible circadian rhythm. Those with more severe trauma had higher levels than those with mild trauma, but a firm correlation with degree of trauma could not be established.

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