drug metabolism in hepatic microsomes was inhibited when urine and feces of rodents were not removed twice daily but permitted to accumulate for 1 week. Inhibition of drug metabolism in rats kept under these conditions may arise from hepatic toxicity due to increased concentrations of ammonia (*5*) in such environments. Ammonia concentrations in animal rooms depend on several factors, including the presence of urease-positive bacteria (*6*), whose population would be related to accumulation of feces. Although filter tops are designed to permit passage of such gases as CO_2 and ammonia out of the cages, filter tops may not perform this task with complete efficiency. Therefore, inhibition of drug metabolism in group 1 of experiment 2 (Table 2) might also arise from hepatic toxicity secondary to ammonia accumulation under filter tops, even with twice-daily changes of the pans under the cages. Even without filter tops, animal rooms would require adequate ventilation to remove ammonia and prevent some of the effects observed when filter tops were used.

Whatever the explanation of our results, they serve to alert investigators to the potential inhibiting effects of dirty environments on hepatic drug metabolism. Clean and dirty conditions had comparatively narrow definitions in these experiments, since animal rooms in different laboratories vary over a wider range of conditions than those employed in our studies; one measure of this extensive range is the large variation in number of times per week or month that cages are cleaned in different laboratories. Dirty environments should now be added to the growing list of factors that affect the extremely sensitive hepatic microsomal system for metabolizing drugs. Among others, these factors include age; sex; strain; litter of origin; painful stimuli; ambient temperature; degree of crowding; time of day or season of drug administration; hormonal, nutritional, and physiological status; and type of bedding (*7*).

ELLIOT S. VESELL
C. MAX LANG, WILLIAM J. WHITE
G. THOMAS PASSANANTI
SPENCER L. TRIPP*
Milton S. Hershey Medical Center, Pennsylvania State University College of Medicine, Hershey 17033

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* Present address: Ciba-Geigy Corporation, Ardsley, New York 10502.

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Amine Metabolites in Human Cerebrospinal Fluid: Effects of Cord Transection and Spinal Fluid Block

Abstract. *Patients with spinal cord transection had normal concentrations of 5-hydroxyindoleacetic acid and low concentrations of 3-methoxy-4-hydroxyphenyl glycol in lumbar cerebrospinal fluid. The presence or absence of spinal fluid block in these patients did not affect concentrations of either amine metabolite. However, the concentration of homovanillic acid was lower in patients with spinal fluid block than in those without block. The results suggest that the spinal cord contributes to concentrations of 3-methoxy-4-hydroxyphenyl glycol and possibly 5-hydroxyindoleacetic acid, but contributes little to that of homovanillic acid in the lumbar spinal fluid of man.*

In an attempt to evaluate brain amine function in man, the concentrations of amine metabolites in the cerebrospinal fluid (CSF) have been studied in a variety of illnesses such as depression, mania, schizophrenia, Parkinson's disease, and dementia. 5-Hydroxyindoleacetic acid (5HIAA), homovanillic acid (HVA), and 3-methoxy-4-hydroxyphenyl glycol (MHPG), the respective metabolites of serotonin, dopamine, and norepinephrine, have received the most attention. Considerable evidence supports the conclusion that brain amine changes are reflected in the concentrations of amine metabolites in ventricular or cisternal CSF (*1, 2*). However, the relation between changes in amine concentrations in the brain and metabolite concentration in the lumbar CSF remains uncertain.

It is likely that HVA in lumbar CSF is derived from sources in the brain because, with the exception of one study (*3*), there is agreement that the spinal cord does not contain appreciable amounts of dopamine (*4–6*). Additional evidence in man comes from Pletscher *et al.* (*7*), who injected [^{14}C]dopamine intravenously and found that peak amounts of labeled HVA in cisternal CSF appeared 2 to 4 hours after infusion, whereas those in lumbar CSF appeared 6 to 8 hours after infusion. Furthermore, Curzon *et al.* (*8*) reported that obstruction to CSF flow in the cervical area was associated with low concentrations of HVA in lumbar CSF.

Little is known about the site of origin of MHPG in the lumbar CSF, and controversy has developed as to whether 5HIAA in the lumbar CSF reflects metabolism in spinal cord rather than in brain. A single injection of 5HIAA into the cistern of cats did not increase 5HIAA concentrations in the lumbar CSF, and values for 5HIAA in the spinal cord after reserpine or serotonin administration closely paralleled those in the CSF (*9*). It was concluded that 5HIAA concentrations in lumbar CSF do not reflect serotonin metabolism in brain. However, several lines of indirect evidence, including accumulation of amine metabolites after probenecid administration and clinicopathologic studies in man (*2*), suggest that some brain contribution to the pool of 5HIAA in lumbar CSF is likely.

In the present study, we investigated the contribution of the spinal cord to the levels of amine metabolites in the CSF of humans. All patients studied had spinal cord transections, and some also had evidence of a block in flow of CSF. Studies of spinal cord transection in rats (*5, 10*), cats (*6, 11*), and rabbits (*12, 13*) suggest that cord serotonin and norepinephrine are localized to nerve endings in descending tracts and that amounts of both amines are dramatically reduced in the cord below the transection. Below the lesion, no serotonin or norepinephrine is recognizable by histofluorescence techniques, and concentrations of amines and their metabolites are reduced to 75 to 86 percent of control values by 1 to 5 weeks after transection.

If similar reductions in spinal cord amines occur after cord transection in man, then it would be expected that metabolites of these amines in CSF would be low in patients with transected spinal cords if the cord normally makes a significant contribution to the levels of amine metabolites in CSF. More-

over, comparison of amine metabolite concentrations in patients with and without blockage of CSF flow should indicate how much metabolite is derived from the spinal cord below the block and how much from sources above the block, including the brain.

Thirteen patients with clinical evidence of complete loss of cord functions below the lesion were studied at the Veterans Administration hospitals in West Roxbury, Massachusetts, and Richmond, Virginia. Six patients had anatomical transections documented at laminectomy, three had physiological transections (no cord discontinuity was visualized), and four had probable anatomical transections but had not had laminectomies. Lumbar punctures were performed between 9 and 11 a.m. with patients in the lateral decubitus position. Patients fasted and had at least 9 hours of bed rest before the lumbar puncture.

The first 8 ml of CSF removed for amine metabolite analysis was immediately frozen. Normal parents of neurological patients and neurological patients without Parkinsonism or spinal cord disease were used as controls and were studied under similar conditions in collaboration with T. N. Chase at the National Institutes of Health (*14*).

The method of Ashcroft and Sharman (*15*) was used to measure 5HIAA, and activation and fluorescence spectra were also determined. This spectral analysis indicated that a true 5HIAA peak could not be identified in three samples with extremely high protein contents, which made valid 5HIAA determinations impossible for these samples (patients 7, 8, and 12 in Table 1). Measurement of HVA was by the method of Gerbode and Bowers (*16*), and MHPG was determined by that of Gordon and Oliver (*17*).

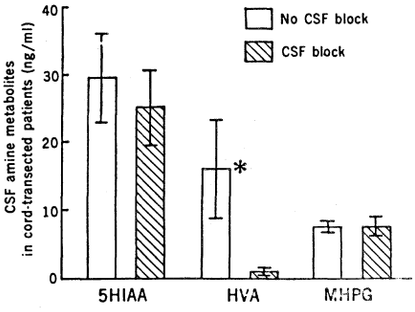

Fig. 1. Amine metabolites in CSF of cord-transected patients with and without CSF block. Patients 3, 4, 6, 10, and 11 had no evidence of CSF block, whereas patients 1, 2, 5, 8, 9, and 12 had evidence of block (elevated protein concentration and positive Queckenstedt test). Patients 7 and 13 did not have Queckenstedt tests. The asterisk indicates that HVA concentrations in patients without CSF block were significantly higher than in those with block ($P < .05$, Student's t-test, one-tailed).

Compared to controls, patients with spinal cord transection had normal 5HIAA concentrations in CSF, but significantly lower values for HVA ($P < .001$) and MHPG ($P < .01$) (Table 1). Eight patients had elevated CSF protein concentrations. White cell counts were normal, while two patients had elevated red cell counts (*18*).

Patients were divided according to whether there was evidence of blockage of CSF flow (elevated protein concentration and positive Queckenstedt test) (*19*) or no evidence of CSF block (normal protein value and negative Queckenstedt test). Hill *et al.* (*20*) document the close relation between CSF block in the spinal subarachnoid space and elevated CSF protein concentration. An elevated protein value in conjunction with an abnormal Queckenstedt test thus suggests that CSF block is present, although the completeness of the block is not accurately established by these methods. Myelograms were not performed after laminectomy.

Patients with apparent blockage of CSF flow in the spinal subarachnoid space had values for 5HIAA and MHPG similar to those of patients without evidence of CSF block (Fig. 1). However, HVA concentrations were lower in patients with restricted CSF flow ($P < .05$, one-tailed) than in patients with apparently normal flow.

No significant differences in amine metabolite values were evident when patients were divided according to duration of the lesion (less than 1 year compared to more than 8 years), level of lesion (paraplegia compared to quadraplegia), or completeness of lesion (anatomic compared to physiological transection).

The lower concentrations of HVA in patients with CSF block than in those without block largely account for the overall low HVA values in the patients with transected cord as compared to controls. These data suggest that HVA

Table 1. Amine metabolites in the cerebrospinal fluid of patients with transected spinal cords; C, cervical vertebra; T, thoracic vertebra.

Patient	Age (yr)	Duration (yr)	Cause	Level	Transection	Protein (mg/100 ml)	Blood cells per high-power field		5HIAA	HVA	MHPG
							White	Red			
1	46	25	Auto	C5	Physiological	216	0	3	16	1	6
2	50	18	Dive	C4-5	Physiological	122	0	61	30	3	11
3	27	0.8	Bullet	T3-4	Complete	31	3	43	26	23	7
4	36	8	Auto	C5-6	Complete	40	0	1	19	32	10
5	64	28	Bullet	T1	Complete	125	1	5	16	0	11
6	22	2	Bullet	C3-4	Physiological	35	1	3	27	8	9
7	50	0.6	Bullet	T8	Complete	>600	0	0	‡	0	†
8	21	0.4	Weight	T11-12	Complete	*	1	0	‡	0	3
9	28	0.25	Bullet	C4-5	Probable	700	0	0	38	1	6
10	24	0.3	Bullet	T1	Probable	19	0	0	18	0	5
11	30	0.5	Auto	C4	Probable	36	0	0	56	§	6
12	24	2	Shrapnel	T1	Complete	*	†	†	‡	0	†
13	52	12	Bullet	T8	Probable	122	0	3744	36	20	7
				Patients: mean ± standard error of mean					28.2 ± 4.0	7.3 ± 3.2	7.4 ± 0.3
				Controls ($N = 29$) ‖					27.3 ± 1.6	22.4 ± 2.4	12.2 ± 1.3
				Difference					Not significant	$P < .001$	$P < .01$

* Xanthochromic spinal fluid. † Insufficient spinal fluid for analysis. ‡ Methodological difficulties (see text). § Salicylate interference. ‖ Studied in collaboration with T. N. Chase.

in the lumbar CSF of man is derived largely from rostral sources and not from the spinal cord. The results are consistent with those of Curzon *et al.* (*8*), who found lower HVA concentrations in CSF of patients with CSF blocks in the cervical region as compared to controls. The low values for HVA in patients with CSF block also are consistent with animal studies showing no appreciable amounts of dopamine in the spinal cord (*4–6*).

The amount of MHPG in the CSF was similar in patients with obstructed CSF flow and in those without block. If brain sources of MHPG make a major contribution to the CSF levels, then one would expect lower amounts of this metabolite in patients with CSF block compared to those without block. This appears to be the first evidence that norepinephrine metabolism in the spinal cord contributes to MHPG levels in the lumbar CSF of man.

The fact that the MHPG values for the total patient group are significantly lower than normal may indicate that a portion of the spinal cord source for MHPG involves descending spinal tracts, which degenerate after transection. It is also possible that the low MHPG values reflect low levels of motor activity in these para- and quadraplegic patients. This would be consistent with the demonstration that experimentally induced increases in psychomotor activity produce higher concentrations of HVA, 5HIAA, and MHPG in CSF of depressed patients (*21*).

Values for 5HIAA were normal in patients with spinal cord transection and were the same whether CSF block was present or absent. Definitive interpretation of these data is difficult without knowledge of serotonin metabolism in the transected human spinal cord. If concentrations of serotonin and 5HIAA in the cord are reduced after transection in man as they are in animals (*5, 6, 10–13*), then the normal 5HIAA values found in the CSF of patients without CSF block would suggest a contribution from rostral sources. However, the limited data in patients with CSF block may indicate that the spinal cord below the level of the block contributes to 5HIAA concentrations in CSF. Although histofluorescence studies in animals detected no serotonin or norepinephrine after transection, the biochemical studies showing residual serotonin in the cord (12 to 25 percent of normal) led to the suggestion that interneurons, which do not degenerate after cord section, are a source of 5HT and 5HIAA (*5, 6, 10–13*). In animals with transected cords, serotonin precursors and antagonists respectively facilitate and inhibit monosynaptic reflexes, results that also provide evidence for a serotonin interneuron (*13, 22*).

In man, the amount of serotonin and 5HIAA remaining in the cord after transection may be greater than in the other species studied. Moreover, the relatively long age of the lesions in this patient population might allow for compensatory increases in serotonin function below the lesion. This, as well as variability in degree of CSF block, might explain the differences between our results and those of Curzon *et al.* (*8*), who found low values for 5HIAA in patients with CSF block.

ROBERT M. POST
FREDERICK K. GOODWIN
EDNA GORDON
Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, Maryland 20014
DONALD M. WATKIN
Veterans Administration Hospital, West Roxbury, Massachusetts 02132

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Carnitine Deficiency of Human Skeletal Muscle with Associated Lipid Storage Myopathy: A New Syndrome

Abstract. *In a rare myopathy muscle fibers contained myriad lipid-filled vacuoles. Homogenates of the patient's muscle oxidized fatty acids more slowly than normal (11 controls). Addition of carnitine increased the oxidation rate with the patient's muscle to the level attained by the controls with carnitine. In five separate muscle samples from the patient the mean carnitine level was less than 20 percent of that observed in 42 controls. Carnitine palmityl transferase and palmityl thiokinase levels in the patient's muscles were not depressed. The present case represents the first recognized instance of carnitine deficiency in human skeletal muscle.*

Carnitine (γ-trimethylamino-β-hydroxybutyrate) catalytically stimulates the oxidative catabolism of long-chain fatty acids by facilitating their transport from the cytoplasm to intramitochondrial sites where they can undergo beta oxidation (*1*). Carnitine deficiency in fetal bovine (*2*), neonatal rat (*3*), or diphtheritic guinea pig myocardium (*4*) and in heart and liver of choline-deficient rats (*5*) is associated with depressed long-chain fatty acid oxidation and excessive triglyceride formation. We here report the first recognized instance of carnitine deficiency in human skeletal muscle with associated lipid storage myopathy.

A 24-year-old woman has been