INCREASED SERUM DOPAMINE-β-HYDROXYLASE ACTIVITY DURING NEUROGENIC HYPERTENSION IN QUADRIPLEGIA

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PATIENTS with high level spinal cord injury, above the sympathetic outflow at the level of thoracic six dermatome very often develop spontaneous hypertensive crises due to any noxious stimuli (GUTTMAN and WHITTERIDGE, 1947). These stimuli usually arise from the urinary bladder due to cystitis or kidney stone formation, or from the rectum because of rectal impaction.

Synthesis of norepinephrine (NE) is catalysed by dopamine-β-hydroxylase enzyme (DBH) from the precursor 3,4-dihydroxyphenylalanine (dopamine) (KAUFMAN and FRIEDMAN, 1965). DBH has been found in the catecholamine containing granules in the heart (POTTER and AXELROD, 1963), synaptosomes of the brain (COYLE and AXELROD, 1942), splenic nerves (STJARNE and LISHAJKO, 1967) and localised in chromaffin granules of the adrenal medulla (MOLINOFF *et al.*, 1970). It is also present in the serum of a variety of mammalian species (WEINSHILBOUM and AXELROD, 1971b). It has been shown that DBH is proportionally released together with neurotransmitter NE by the process of exocytosis (WEINSHILBOUM *et al.*, 1971a). Furthermore, adrenalectomy in rat was found not to alter the base line levels of serum DBH (WEINSHILBOUM *et al.*, 1971b).

An increase in HVA output (SMITH and DANCIS, 1967) and a decrease in serum DBH activity has been demonstrated in familial dysautonomia (FREEDMAN *et al.*, 1972; WEINSHILBOUM and AXELROD, 1971a). It has also been shown that catecholamine metabolites were significantly enhanced during hypertension in chronic quadriplegia (NAFTCHI *et al.*, 1971; SELL *et al.*, 1972). Serum DBH activity, therefore, was analysed in chronic quadriplegic subjects as an index of sympathetic activity.

METHODS

A group of eight quadriplegic patients were self-compared before and after expansion of the urinary bladder by means of water intake. All patients were during the chronic phase, 6 months or longer after the onset of the injury, and had suffered a complete physiologic transverse lesion at the level of the 5th and 7th cervical dermatomes (C_5–C_7). Brachial blood pressure was measured by auscultatory technique and digital blood flow was measured calorimetrically in the fourth finger.

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TABLE 1. SERUM DOPAMINE-β-HYDROXYLASE ACTIVITY AND URINARY CATECHOLAMINE METABOLITES BEFORE AND DURING HYPERTENSIVE CRISES IN SPINAL MAN

No. of subjects	Brachial blood pressure (mmHg)		VMA*		HVA*		HMPG*		DβH†	
	Before	During	Before	During	Before	During	Before	During	Before	During
1	108/68	230/130	1·5	5	2	10	2	6	718	1652
2	144/102	210/126	3	7	6	16	4	8	1155	1916
3	128/80	176/122	3	5	4	7	2	3	594	646
4	136/98	172/110	2·5	5	6	12	3	5·5	1394	1617
5	112/78	150/90	1	2·5	2	5	2	4	307	484
Mean	126/85	188/116	2·2	4·9	4·0	10	2·6	5·3	833	1263
± S.D.	—	—	0·91	1·6	2·0	4·3	0·89	1·9	437	650
P				>0·001		>0·001		>0·001		>0·05

* μg/mg creatinine.
† nmoles phenylethanolamine/ml serum/hr.

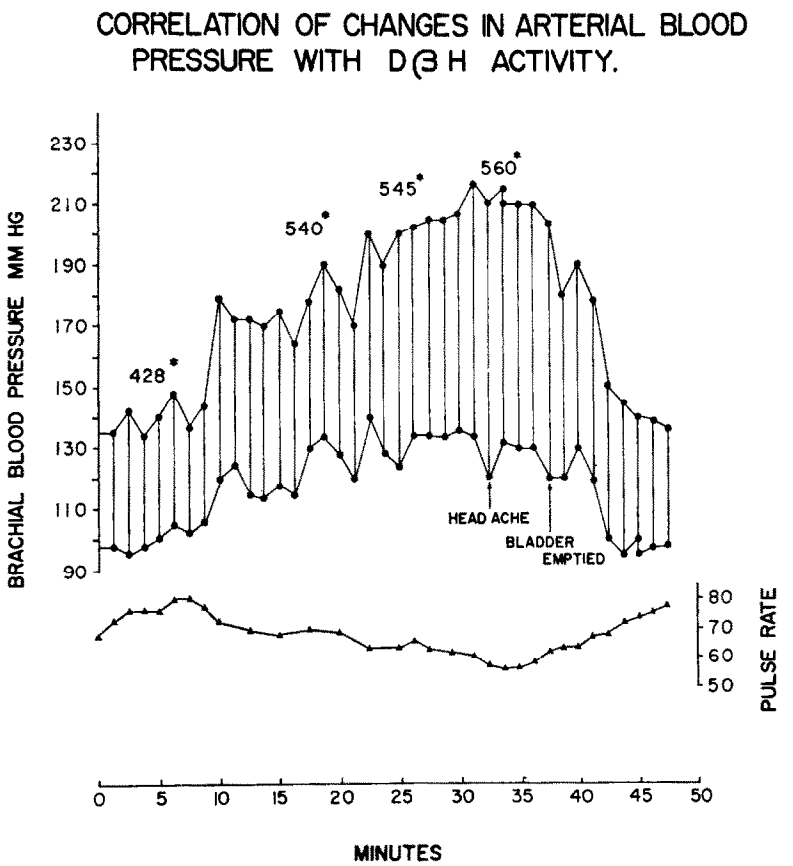

FIG. 1.—Numbers represent DβH (nmoles phenylethanolamine formed/ml serum/hr)

Serum DBH activity was analysed before and during the height of hypertension. Serum DBH activity was also determined in five patients during spontaneous hypertensive crises and at the time when the patients' blood pressure was at resting control levels. Serum DBH activity was determined by a modification (WEINSHILBOUM and AXELROD, 1971a) of the sensitive isotopic method of MOLINOFF *et al.* (1970). In addition, urine specimens from the five quadriplegic subjects were collected just before, during or immediately after a spontaneous hypertensive crisis.

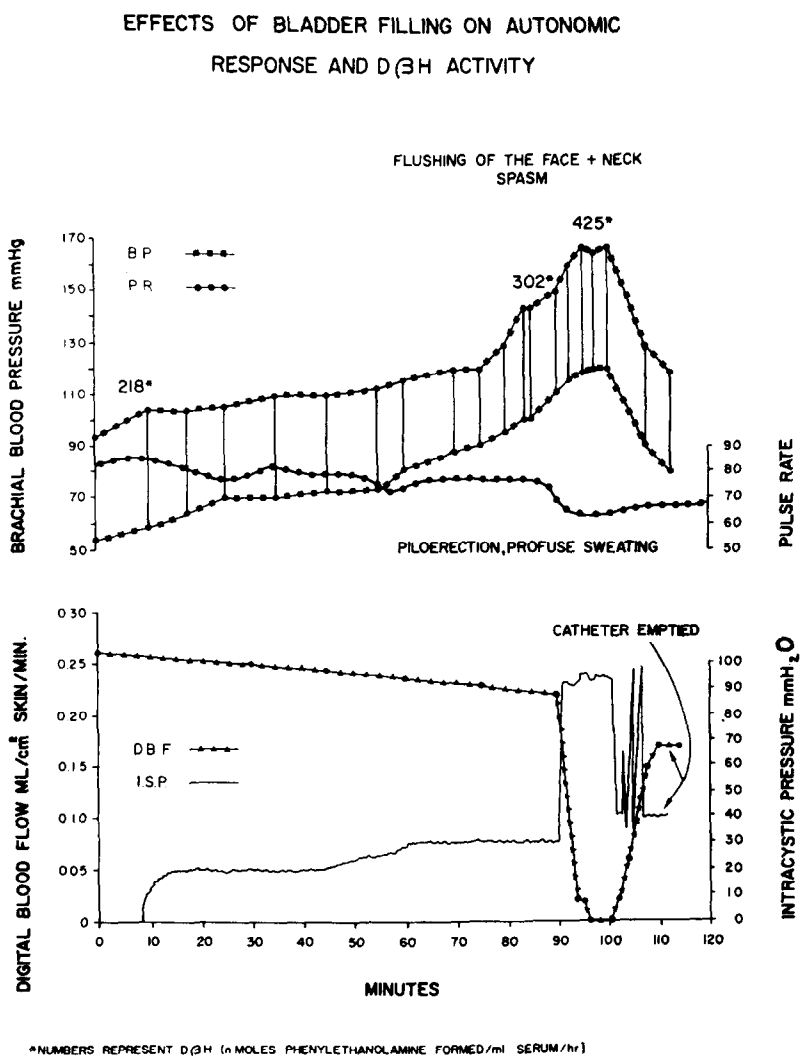

FIG. 2.—Crystometric studies were performed in a C_7 quadreplegic man. Note that the height of the DBH activity coincides with that of brachial and intracystic pressure, at which time the digital blood flow has dropped to immeasurable amounts and pulse rate is at its lowest level.

BP = Brachial blood pressure PR = Pulse rate
DBF = Digital blood flow ISP = Intracystic pressure

Urine samples were analysed for their content of catecholamine metabolites, 4-hydroxy-3-methoxymandelic acid, vanillmandelic acid (VMA), 4-hydroxy-3-methoxyphenylacetic acid, homovanillic acid (HVA), and 4-hydroxy-3-methoxyphenylethylene glycol (HMPG). VMA and HVA were analysed by bidimensional paper chromatography (ARMSTRONG *et al.*, 1956) and HMPG was analysed by gas–liquid chromatography (WILK *et al.*, 1967).

RESULTS

In five C_7-C_8 quadriplegic subjects who developed spontaneous hypertensive crises (Table 1) the mean brachial blood pressure rose from a resting value of 126/85 mmHg to 188/116 mmHg. The mean values for each CM metabolite, expressed in micrograms per milligram of creatinine in urine, increased significantly during hypertensive crisis ($P < 0{\cdot}001$). Such high values are found only in patients with pheochromocytoma or neuroblastoma. Similarly, serum DBH was significantly enhanced during hypertension (Table 1).

In one C_5-C_6 subject, during the expansion of the urinary bladder, the gradual rise in arterial blood pressure is accompanied by progressive increase in serum DBH activity and a decrease in pulse rate (Fig. 1). In another C_7 quadriplegic subject it is demonstrated that the height of arterial blood pressure coincides with that of DBH activity and intracystic pressure (Fig. 2). At this point of maximal autonomic activity the pulse rate decreases markedly and the digital blood flow drops to immeasurable amounts.

CONCLUSIONS AND SUMMARY

Autonomic response in quadriplegia is manifested by headache, piloerection, a red flush, and profuse diaphoresis above the level of transection. In contrast to the vasodilatation cephalad to the lesion, there is a marked vasoconstriction of peripheral blood vessels (Fig. 2) and pallor of the skin below the level of transection. The hypertension, brought about spontaneously or by means of water intake, is caused by increased elaboration of catecholamines. The concentration of homovanillic acid, the major metabolite of dopamine, was enhanced significantly concomitant with that of other catecholamine metabolites and with enhanced activity of serum DBH. In agreement with previous *in vitro* studies (WEINSHILBOUM *et al.*, 1971), these results indicate an *in vivo* proportional release of the neurotransmitter NE with DBH possibly by the process of exocytosis.

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