1B (traces B to I) were recorded in two groups with a four-channel Medilog (Oxford Instruments) recorder.

11. Several smoothing time constants were used to obtain a measure of the kinetic content of different EMG patterns. For the present data, a time constant of 150 msec was used. A correction was made to the data on percentage of time active for the orbicularis oculi because the very short duration of the EMG bursts during eye blinks caused slight (10 percent) widening of the envelope, relative to the unsmoothed |EMG|. The computer sampling rate was 100 Hz in real time.
12. M. A. Johnson, J. Polgar, D. Weightman, D. Appleton, *J. Neurol. Sci.* **18**, 111 (1973).
13. For the large muscles for which superficial and deep biopsy data were reported, superficial data were selected for muscles from which recordings were made with surface electrodes.
14. D. C. King and K. M. Michels, *J. Exp. Psychol.* **53**, 113 (1957). Blink |EMG| duration was found to vary from 0.04 to 0.15 second. There were spontaneous tenfold variations in blink amplitude and rate in some individuals. A detailed account of the eye-blink data will be published (A. W. Monster, H. C. Chan, D. O'Connor, in preparation).
15. Similar type I percentages for the biceps brachii have been published elsewhere [M. H. Brooke and W. K. Engel, *Neurology* **19**, 221 (1965); Edström and Nyström (*3*)]. One possible explanation for the systematic deviation of the biceps brachii data in Fig. 2 is that a small percentage of superficial low-threshold motor units dominates the measurement of percentage of time active in this muscle. This explanation is supported by an analysis of the |EMG| amplitude distribution but contradicted by data on the usual intramuscular distribution of fiber types [item (i) in (*7*)].
16. The assumptions are that (i) fibers (or, rather, motor units) are consistently activated in the same way [E. Henneman, G. Somjen, D. O. Carpenter, *J. Neurophysiol.* **28**, 560 (1965); A. W. Monster and H. Chan, *ibid.* **40**, 1432 (1977)]; (ii) type I fibers are recruited before type II fibers; (iii) |EMG| amplitude is linearly related to the percentage of muscle fibers active [H. S. Milner-Brown and R. B. Stein, *J. Physiol. (London)* **246**, 549 (1975)]; and (iv) the |EMG| amplitude distribution, based on 8 hours of observation, is representative of the normal distribution of activity states of the muscle [item (ii) in (*7*)].
17. Intuitively, we expected T_A times to be correlated with the twitch contraction times of muscles; slowly (rapidly) contracting fibers need proportionally longer (shorter) T_A times to develop force. This intuitive bias is supported by a limited amount of human twitch contraction time data [F. Buchtal and H. Schmalbruch, *Acta Physiol. Scand.* **79**, 435 (1970); A. J. McComas and H. C. Thomas, *J. Neurol. Sci.* **7**, 301 (1968)]. The observed correlation between T_A time and percentage of type I fibers is thus in accordance with more fundamental findings [M. J. Barany, *J. Gen. Physiol.* **50**, 197 (1967)] relating fiber type to the speed of contraction of muscle fibers.
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3-Methoxy-4-Hydroxyphenylglycol in Cerebrospinal Fluid and Vanillylmandelic Acid in Urine of Humans with Hypertension

Abstract. *3-Methoxy-4-hydroxyphenylglycol (MHPG) was measured in lumbar spinal fluid of 20 subjects with hypertension of varied etiology and severity. There was a significant correlation between the concentration of MHPG and the severity of hypertension. However, changes in the concentration of vanillylmandelic acid in the urine of these subjects were insignificant. In six subjects, administration of clonidine or α-methyldopa, two centrally acting antihypertensive drugs, was associated with a significant lowering of MHPG concentrations. These data support the hypothesis that central catecholamines are involved in clinical hypertension.*

The peripheral catecholamines do not seem to cross the blood-brain barrier (*1*). It appears that the brain catecholamine pool is distinct and unrelated to the peripheral biosynthesis of the amines. Catecholamines appear to have a neurotransmitter role in the brain (*2*). Noradrenaline (NA)-containing neurons (*3*), and more recently adrenaline-containing neurons (*4*), have been located in areas of the brain that are intimately concerned with cardiovascular control. Hence, a change in the activity of the catecholaminergic neurons may be reflected in disordered cardiovascular function.

Alterations of central catecholamine turnover, indicating altered rates of central release of the amines, have been observed in various types of experimental hypertension (*5*). Intraventricular injections of 6-hydroxydopamine, which selectively destroys central catecholaminergic neurons, prevented the development of experimental hypertension as well as spontaneous hypertension of rats (*6, 7*). The activity of tyrosine hydroxylase, the rate-limiting enzyme in the biosynthesis of catecholamines, was significantly reduced in the pontine locus coeruleus of patients with idiopathic orthostatic hypotension and Shy-Drager syndrome (*7, 8*).

Because there are few reports on the role of central catecholamines in human hypertension, we explored the possible involvement of brain catecholamines in clinical hypertension. To assess indirectly the rates of catecholamine turnover in the brain, we measured the concentration of 3-methoxy-4-hydroxyphenylglycol (MHPG), the major metabolite of brain NA and adrenaline in lumbar cerebrospinal fluid (CSF) according to a spectrophotofluorometric method of Korf *et al.* (*9*). To assess the peripheral catecholamine turnover, we estimated the amount of vanillylmandelic acid (VMA) excreted in the urine over 24-hour periods by means of the colorimetric method of Sunderman *et al.* (*10*).

Twenty patients with renal (*10*) and essential (*11*) hypertension of varying severity, and with blood pressures of 160/95 mm-Hg or above, were studied (13 males and seven females; age range 25 to 59 years, mean age 41.5 years). Eight patients with iron deficiency anemia (hemoglobin 9 to 11 g per 100 ml) recovering from ankylostomiasis were used as controls (five males and three females; age range 20 to 50 years, mean age 39.3 years). The blood pressures of the control subjects ranged from 120/75 to 130/85 mm-Hg, and they showed no evidence of any other disease. All the patients and the controls were of local Indian ancestry. All the patients with hypertension were subjected to detailed clinical and laboratory evaluation to determine the etiology and severity of their disease and its effects on the target organs.

Cerebrospinal fluid (10 to 15 ml) was obtained by lumbar puncture from all of the 28 subjects 7 to 15 days after they were admitted to the hospital. The CSF was stored at −20°C. The sample was discarded if blood was found in the CSF. The recoveries of the standard MHPG solutions were of the order of 70 to 80 percent. The amount of MHPG in the CSF was calculated by comparison with our standard recovery graph.

Six of the 20 patients with hypertension were chosen at random to be treated with clonidine or α-methyldopa so that we could study the effect of centrally acting antihypertensive drugs on the metabolites of central and peripheral

Table 1. Concentrations of MHPG in the CSF and urinary VMA excretion rates in control subjects and patients with hypertension. Urinary VMA was estimated in seven out of eight controls and 14 out of 19 patients with hypertension. One of the 20 patients with hypertension, in whom the disease was severe, had a very high concentration of MHPG (133 ng/ml) and was excluded from statistical analysis.

Group	MHPG (ng/ml)		VMA (mg/24 hours)	
	Number of subjects	Mean ± S.D.	Number of cases	Mean ± S.D.
Control	8	34.12 ± 11.32	7	4.08 ± 1.27
Hypertensive	19	53.00 ± 6.32*	14	4.89 ± 1.49†

*$P < .001$. †$P > .03$.

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Table 2. The effect on blood pressure and MHPG concentrations of 7 days of treatment with clonidine or α-methyldopa in six patients with hypertension.

Patient	Blood pressure		MHPG (ng/ml)				P
	Before treatment	After treatment	Before treatment		After treatment		
			MHPG	Mean ± S.D.	MHPG	Mean ± S.D.	
			Clonidine				
1	185/115	140/100	54		30		
2	210/135	160/105	61	56.6 ± 3.09	24	35.3 ± 12.03	< .05
3	190/120	175/100	55		52		
			α-Methyldopa				
4	195/120	170/105	54		47		
5	220/125	165/110	60	53.6 ± 5.3	38	39.6 ± 5.43	< .05
6	170/105	145/95	47		34		

catecholamines. Three of these patients were given clonidine hydrochloride and the remaining three α-methyldopa in dosages of 150 to 600 μg and 750 to 1500 mg per day, respectively. Both of these drugs were given in three equally divided doses for 7 days. The blood pressure after treatment was recorded and the MHPG in the CSF as well as the urinary VMA excretion rates were reestimated.

The concentration of MHPG in controls was 34.12 ± 11.31 ng/ml (Table 1) and was not related to age or sex. Korf *et al.* (*9*) reported similar values (29 ± 14 ng/ml). The mean concentration of MHPG in hypertensive subjects was 53.0 ± 6.32, which was significantly higher than the control values ($P < .001$) (Table 1). Although there was some degree of overlap among the individual values of the two groups, the concentrations of MHPG in all the patients with hypertension were in the higher limits of the control values (Fig. 1). The MHPG values were significantly correlated with the severity of hypertension ($r = .74$). The age and sex of the patients, and the etiology, duration, and complications of hypertension were not related to the MHPG concentrations.

The mean urinary VMA excretion rate in control subjects was 4.08 mg/24 hours (range 2.5 to 6.2 mg/24 hours), whereas Sunderman *et al.* (*10*) obtained values of 4.10 mg/24 hours (range 0.7 to 6.8 mg/24 hours) in their cases. The mean urinary VMA excretion rate in the patients with hypertension was 4.89 ± 1.49 mg/24 hours, which was not statistically higher than the control value ($P > .03$).

The treatment with clonidine or α-methyldopa resulted in statistically significant decreases ($P < .05$) in MHPG concentrations (Table 2). There was a significant correlation between the percentage decrease in the MHPG concentration and percentage decrease in the mean blood pressure ($r = .77$).

Because the concentrations of NA and adrenaline and their metabolites in the CSF (with the exception of MHPG) are too low to be measured accurately, the estimation of MHPG, a selective but common metabolite of NA and adrenaline in the central nervous system appears to be the only suitable means of assessing the brain catecholamine turnover in clinical situations (*10*). However, at present we have no means of determining whether the increased MHPG observed in hypertension arises from brain adrenaline or NA.

Recent studies (*12*) show that activation of α-adrenoceptors by adrenaline at different levels in the CNS (hypothalamus, brainstem, and spinal cord) leads to a hypertensive response. The finding in rats of increased amounts of the adrenaline-forming enzyme, phenylethanolamine *N*-methyltransferase, in genetic (spontaneous) and experimental hypertension (*13*) is consistent with increased adrenaline turnover in hypertension. In view of these data, it appears that increased adrenaline turnover may account for the increased MHPG concentrations in clinical hypertension.

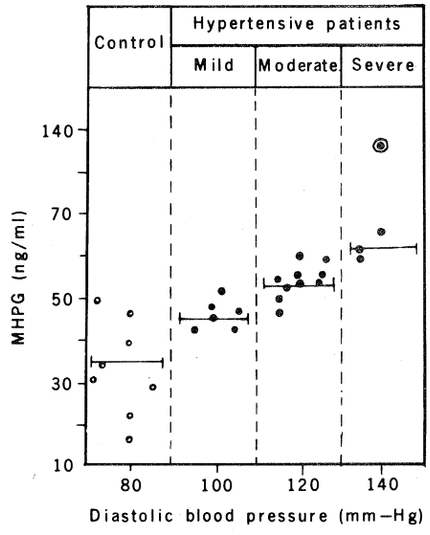

Fig. 1. Individual MHPG concentrations and their relation to diastolic blood pressure in 20 patients with hypertension. Open circles show the values from eight control subjects; solid circles show the values for hypertensive patients. Horizontal lines depict mean values in each group. One patient with severe hypertension and a relatively higher concentration of MHPG (133 ng/ml, shown by ⊙) was excluded from the statistical evaluation.

Our results point toward a definite involvement of central catecholamines in human hypertension, and further investigations of this interrelation between central catecholamines and human hypertension are clearly warranted.

R. K. Saran, R. C. Sahuja
N. N. Gupta, M. Hasan
Department of Medicine, King George's Medical College, Lucknow University, Lucknow, India

K. P. Bhargava
K. Shanker, K. Kishor
Department of Pharmacology and Therapeutics, King George's Medical College

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14. All procedures in these experiments were done with the patients' informed consent.

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