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Urinary Phenols in Patients Treated with α-Methyldopa

SIR,—There is still some doubt about the mode of action of the hypotensive drug α-methyldopa.

It was originally introduced because Sourkes (1954) had shown that in high concentration it blocked the conversion of dopa to dopamine by inhibiting dopa decarboxylase and thus inhibiting catecholamine formation.

Other workers (Gillespie and others, 1962; Pletscher, 1963) have suggested that α-methyldopa's hypotensive action is due to its reserpine-like property of depleting the body stores of catecholamines.

Recently, Day and Rand (1963) suggested that it inhibited the conversion of dopa to dopamine by competing for dopa decarboxylase, being itself converted to α-methyldopamine. This, in turn, was converted to α-methylnoradrenaline which displaced noradrenaline from the storage sites at sympathetic nerve endings. Here it was held as a "false neurotransmitter" and was released in response to sympathetic nerve stimulation. Having a pressor activity much less than that of noradrenaline, the blood pressure fell.

It seemed likely that a study of the urinary excretion of the metadrenalines and the phenolic acids 4-hydroxy-3-methoxymandelic acid (HMMA) and homovanillic acid (HVA) after the administration of α-methyldopa might throw some light on this problem.

Hypertensive patients were fasted overnight. A control sample of urine was collected over a period of 2 hr. The patient was then given an oral dose of DL-α-methyldopa (usually 250 mg.) and no food was allowed for a further 4 hr.

Urine samples were collected over successive 2 hr. periods for 8 to 12 hr. The patient remained in bed throughout the test.

Phenolic acids were extracted and separated by two dimensional chromatography as described by Robinson and others (1959). The metanephrines were isolated by the method of Robinson and Smith (1962), separated chromatographically, and estimated spectrophotometrically after their oxidation to vanillin.

Two hours after the administration of the α-methyldopa the HVA excretion had fallen to about 50 per cent of that in the control period. Two hr. later, it could scarcely be detected on the chromatogram and 8 hr. after giving the α-methyldopa, HVA was undetectable on the chromatogram.

During the same period there was a slight rise in the excretion of HMMA and a significant rise in the excretion of the metadrenalines.

About 10 to 12 hr. after the dose of α-methyldopa, a compound appeared in the urine which was tentatively identified as α-methylnormetanephrine.

Our results are in accord with Day and Rand's hypothesis. The early reduction in HVA excretion reflects the dopa decarboxylase inhibition at this stage. The increased excretion of both metadrenaline and normetadrenaline

suggests that both adrenaline and noradrenaline may be displaced by their α-methyl homologues. The fact that α-methylnormetanephrine does not appear in the urine for 10 to 12 hr. is consistent with the α-methylnoradrenaline's being held at nerve endings until the noradrenaline is displaced.

A further point of interest was that there was a striking increase in the excretion of vanillic acid during these experiments. Eight hr. after the α-methyldopa was given, the vanillic acid excretion was about ten times greater than in the control period. The acid could not have arisen from exogenous sources since the patients were fasted for the early part of the test and the food taken later was known to be free from sources of vanillic acid.

This observation suggests that vanillic acid can arise from α-methylnoradrenaline by an analogous series of reactions to that in which it is known to arise from noradrenaline (Smith and Bennett, 1958; Rosen, and Goodall, 1962).

The results of these studies will be published *in extenso* at a later date.

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Effects of Reserpine in Rats Pretreated with α-Methyldopa

SIR,—Day and Rand (1963a) have described an arousing effect of α-methyldopa in rats sedated by reserpine. It was assumed that, when the brain stores of dopamine and noradrenaline had been emptied by reserpine, there was a repletion by the α-methylated catecholamines formed from α-methyldopa. Carlsson and Lindqvist (1962) have shown that α-methyldopa is decarboxylated *in vivo* and that α-methyldopamine is transformed into α-methylnoradrenaline in the brain. It was suggested by Day and Rand (1963b) that the α-methylated catecholamines may serve as "false transmitters", probably with a less potent activity than the natural amines.

In the present study we have further demonstrated a central action of the α-methylated catecholamines by pretreating rats with α-methyldopa before a depletion of the catecholamine stores is produced by reserpine.

The rats, weighing 300 g. were given α-methyldopa (Aldomet, Merck, Sharp and Dohme Ltd.) 150 mg./kg. intraperitoneally at 9 a.m. on the first and second days, followed by 300 mg./kg. at 4 p.m. on the second day. On the third day these pretreated rats, together with untreated control rats, were given reserpine, 2 mg./kg. i.p. Before the reserpine injection all animals appeared normal.