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Relation of the Mecholyl Test to Catecholamine Excretion.* (26503)

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The mecholyl (methacholine) test has been proposed as a measure of sympathetic tone (1). Funkenstein(2) postulated that the differences in reactivity of the systolic blood pressure in human subjects to injection of mecholyl was related to the relative excretion of epinephrine and norepinephrine. He suggested that those subjects whose blood pressures returned rapidly to the base line after injection of mecholyl had reacted by producing more norepinephrine; in contrast, those whose blood pressures stayed low for a long period were assumed to produce more epinephrine in response to stress. Elmadjian (3) studied urinary excretion of epinephrine and norepinephrine and was able to correlate the mecholyl area with the excretion of norepinephrine but not with epinephrine. Manger(4) studied the blood level of epinephrine and norepinephrine and could demonstrate no change in these levels with injection of mecholyl. Since we have been able to standardize the procedure and interpretation of the mecholyl test(5), it seemed appropriate to reinvestigate the relationship between the urinary excretion of the active catecholamines and mecholyl area.

Methods. The mecholyl test was carried out as outlined previously(5). Subjects were patients at Hillside Hospital, a voluntary psychiatric institution. They were seen early in their hospital stay, and were not receiving specific medication at the time of study. In all, 48 patients were studied. Each was tested under basal conditions. A urine sample was collected prior to the test. The patient then rested for at least a half-hour during which time his blood pressure was automatically recorded at intervals of one minute by a recording sphygmomanometer. When the pressure was noted to be steady, an injection of 1 cc of mecholyl (10 mg) was given subcutaneously. The change in pressure was recorded over the next 20 minutes. A urine sample was then collected. The mecholyl area was determined by plotting systolic pressure *vs.* time in minutes on graph paper (10 squares/cm) and measuring the area enclosed by means of a compensating polar planimeter. The area was corrected for the basal blood pressure as previously described.

For control purposes, the mecholyl test procedure was repeated in 10 selected patients using 1 cc of normal saline (subcutaneous) instead of mecholyl. Blood pressure areas and urine analyses were conducted as for the standard test.

Chemical analyses. Urine specimens (25-50 cc) were analyzed for epinephrine and norepinephrine by the fluorometric method of von Euler and Floding(6). Creatinine content was determined simultaneously, and catecholamine output calculated as μg/g creatinine.

Observations. In the 10 control studies in which saline alone was injected (Table I), there was relatively little change in blood pressure as manifested by areas generally

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TABLE I. Excretion of Epinephrine and Norepinephrine in Urine Following Injection of Saline (1 cc) and Mecholyl (10 mg).

	Saline							Mecholyl						
Pt.	Area	NE	NE′	NE′/NE	E	E′	E′/E	Area	NE	NE′	NE′/NE	E	E′	E′/E
1	+8.5	35.3	116.0	3.3	2.4	1.3	.5	−20.8	21.3	91.2	4.3	5.9	21.5	3.6
2	+4.5	18.8	19.7	1.0	6.9	12.8	1.9	+71.5	22.1	21.5	1.0	9.1	18.5	2.0
3	− .8	43.0	50.2	1.2	12.1	9.3	.8	−16.4	8.8	27.1	3.1	5.8	7.8	1.3
4	+3.6	59.6	40.8	.7	14.0	19.2	1.4	−28.5	16.0	18.3	1.1	19.2	22.6	1.2
5	−5.5	32.6	67.5	2.1	7.3	3.1	.4	−29.5	16.5	14.0	.9	17.7	26.9	1.5
6	+2.6	12.0	9.5	.8	6.5	2.6	.4	−20.8	9.0	9.2	1.0	1.7	5.0	2.9
7	−2.5	17.8	24.5	1.4	10.3	9.6	.9	+24.8	10.4	35.3	3.4	2.0	10.3	5.1
8	+1.5	16.4	12.5	.8	2.2	2.3	1.0	+ 9.2	11.6	20.2	1.7	3.4	2.9	.9
9	−14.1	27.0	41.3	1.5	7.3	19.9	2.7	− 7.8	75.4	63.9	.8	6.7	6.9	1.0
Avg				1.4			1.1				1.9			2.2

Area = Cm^2 area enclosed by curve of systolic blood pressure for 20 min. after inj. NE = Excretion of norepinephrine before inj. expressed as $\mu g/g$ creatinine. NE′ = Excretion of norepinephrine after inj. expressed as $\mu g/g$ creatinine. E = Excretion of epinephrine before inj. expressed as $\mu g/g$ creatinine. E′ = Excretion of epinephrine after inj. expressed as $\mu g/g$ creatinine.

well within the range of ± 10 cm^2. Norepinephrine tended to rise after injection of saline to give a post-to-pre excretion ratio of 1.4. Average epinephrine excretion was virtually unaltered (ratio. 1.1). This compares with ratios after mecholyl injection of 1.9 for norepinephrine and 2.2 for epinephrine. The statistical significance of these numbers is relatively low in view of the small number of tests.

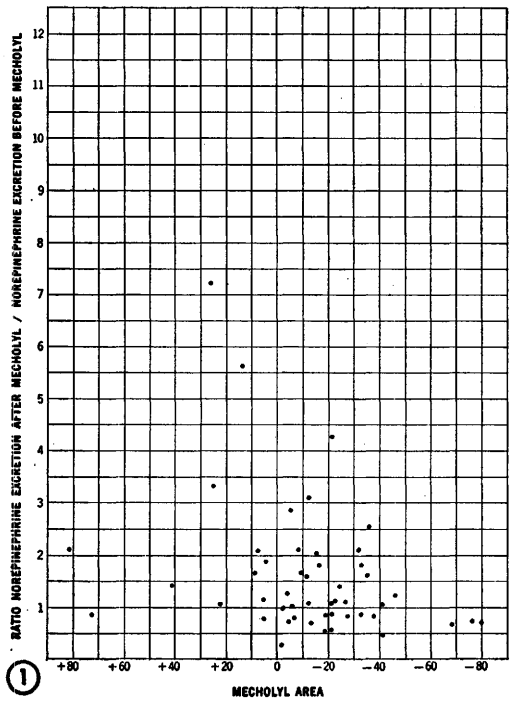
Analysis of the entire group of mecholyl tests revealed a fairly consistent increase in norepinephrine and epinephrine excretions. The mean ratio of norepinephrine excretion after mecholyl injection to the basal value was 1.65. The mean ratio for epinephrine excretion was 2.04.

The correlation of the ratio of norepinephrine excretion before and after mecholyl is presented in Fig. 1. While there is a fairly scattered distribution of these values, the Pearson's product moment coefficient has been calculated to be 0.306, with a standard error of ± 0.13. Values for the ratio of epinephrine excretion before and after mecholyl are graphed against the mecholyl area in Fig. 2. The correlation here is much poorer, with a Pearson's product moment coefficient of 0.101, standard error ± 0.14.

The correlation of mecholyl area against age was calculated for this group of patients to be 0.486 ± 0.11, which is significant at the 0.05 level.

Discussion. Armstrong and McMillan(7), Axelrod(8), and Kirshner *et al.*(9) have demonstrated several 3-0-methylated metabolites in urine which are derived from epinephrine and norepinephrine. It is estimated that about 50% of administered epinephrine is converted to metanephrine (free and sulfate-bound) in humans. 3,4-Dihydroxymandelic acid and 3-methoxy-4-hydroxymandelic acid represent 40% of the residual metabolites. These compounds are not measured by the fluorometric technic employed for catecholamine analysis. The chemical assay of epinephrine and norepinephrine in the urine thus represents only a small fraction, possibly 3%, of the original amounts of these compounds. As a consequence, minor alterations in production of the major metabolites would be expected to incur highly significant changes in the measured excretion of the unaltered catecholamines. Any conclusions drawn from excretion studies of the unchanged hormones must be reviewed in the light of these basic considerations.

The finding of any correlation between the values for norepinephrine and epinephrine excretion and any other parameter must then be considered suggestive. Although the correlation of norepinephrine excretion with the mecholyl area is at the limit of statistical significance, it is not inconsistent with the theoretical assumption that the mecholyl test is an index to sympathetic hyperreactivity, and that norepinephrine excretion levels are in some way related to mecholyl reactivity. The posi-



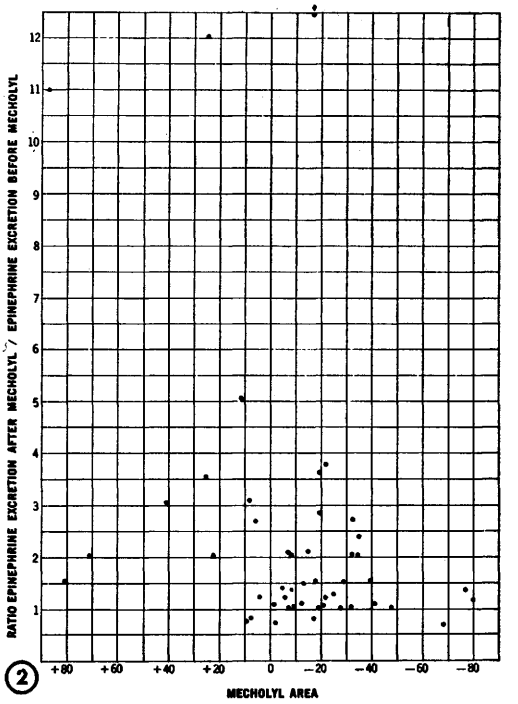


FIG. 1. Relationship of mecholyl area to ratio of norepinephrine excretion.
FIG. 2. Relationship of mecholyl area to ratio of epinephrine excretion.

tive (albeit poor) correlation between the trend in the mecholyl area and the norepinephrine excretion ratio also fits in with the concept that higher reactivity of the sympathetic nervous system is related to norepinephrine production. The poorer correlation with epinephrine allows no conclusion to be drawn other than that when mecholyl is given excretion of epinephrine is increased. Correlation coefficients between the epinephrine and norepinephrine ratios and age were poorer than those with the mecholyl area.

The fact that any correlation between mecholyl areas and excretion patterns of epinephrine and norepinephrine exists must be considered significant in view of the relatively small fraction of the amount of these substances produced which can be measured. If the quantity of metanephrine and normetanephrine could be studied, it might be expected to give a more accurate index of production of the pressor substances in response to the mecholyl stress.

Summary. Following injection of mecholyl, excretion of epinephrine and norepinephrine tends to increase. Excretion ratios for norepinephrine and for epinephrine were compared with the relative change in blood pressure after injection of mecholyl. There is a correlation of low statistical significance between norepinephrine excretion ratios and mecholyl area, which suggests that the more hypertensive responses to mecholyl may be associated with higher norepinephrine reactivity.

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