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### Research Article

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# Biochemical and Pharmacologic Effects of $\alpha$ -Methyltyrosine in Man

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**ABSTRACT** Alpha methyltyrosine ( $\alpha$ -MPT) was administered to 52 patients from 4 days to 10 months; 22 patients were cases of pheochromocytoma and 20 had essential hypertension. Inhibition of catecholamine synthesis in the range of 50–80% was achieved with divided daily drug dosage of from 1.0 to 4.0 g. Striking clinical benefit was noted in patients with pheochromocytoma in whom the drug was used in preparation for surgery and during chronic medical management. The drug appeared to have limited usefulness when used in essential hypertension, unless added to existing therapy with conventional agents. No beneficial effects were noted in thyrotoxicosis, glaucoma, and Raynaud's phenomenon. Untoward effects in order of decreasing incidence were: sedation (with insomnia on withdrawal), anxiety, tremor, diarrhea, and galactorrhea. Drug crystalluria, which has been observed in animals and is currently restrictive of clinical trials, was not observed in these studies. Evidence is presented that the minor conversion of  $\alpha$ -MPT to methyl dopa probably does not contribute significantly to the central and peripheral effects of the drug.

## INTRODUCTION

Of various methods employed for modifying the functions of the sympathetic nervous system, a unique and recently successful one has been the inhibition of catecholamine biosynthesis by  $\alpha$ -methyl-*para*-tyrosine ( $\alpha$ -MPT) (1–3). Studies on the metabolic fate of  $\alpha$ -MPT reported in the

previous paper (4) have indicated that the drug is adequately absorbed from the gastrointestinal tract and that the degree of inhibition achieved in man approximates the values which could be predicted from the plasma levels of the drug. In the earlier clinical studies (2, 3), maximal doses of drug generally were not administered. Nonetheless, the drug seemed to have therapeutic potential in patients with pheochromocytoma, whereas the results in cases of essential hypertension did not suggest beneficial effects.

This paper presents the results of our total clinical experience with  $\alpha$ -MPT and includes findings with larger doses of drug and longer durations of therapy than used previously. In addition to cases of pheochromocytoma and essential hypertension, patients with open angle glaucoma, thyrotoxicosis, migraine, and Raynaud's phenomenon were studied since it seemed that alteration of catecholamine synthesis in these disorders might lead to therapeutic benefit. Selected pharmacological studies were performed which bear on the mechanism of action of  $\alpha$ -MPT. Due to limitations imposed on clinical use of  $\alpha$ -MPT some of the observations were necessarily preliminary.

## METHODS

The subjects were patients hospitalized with the following diseases: (a) pheochromocytoma: 15 patients with benign and 7 with malignant tumors; (b) essential hypertension: 20 patients with uncomplicated disease; (c) other disorders: 1 patient with thyrotoxicosis, 1 with migraine headache, 6 patients with Raynaud's phenomenon (5 definite, 1 suspected to be related to scleroderma), and 2 with open angle glaucoma. Identical capsules containing 100 or 250 mg of alpha methyl-L-*para*-tyrosine or placebo

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material<sup>1</sup> were administered orally to the patients every 6–8 hr for periods of 4 days to 10 months; total daily doses were as high as 4000 mg. The majority of patients received the drug for 2–4 wk. Some patients with pheochromocytoma were receiving phenoxybenzamine to control symptoms, and this drug was usually not withdrawn until definite therapeutic effects of the  $\alpha$ -MPT were observed. The antihypertensive effects of  $\alpha$ -MPT were investigated adequately in 13 of the patients with essential hypertension. In these patients drug dosage was increased from initial levels of 0.5–1.0 g daily to a maximum of 3.0 g as required for reduction of blood pressure unless limited by untoward effects. Pretreatment control periods in these cases varied from 7 to 21 days, treatment periods from 6 to 21 days (average of 12), and post-treatment observations were made through at least 5 days after loss of drug effect if hospitalization time permitted. Placebo capsules were administered during the pre and posttreatment periods in the same doses as initial and final doses of  $\alpha$ -MPT.

Blood pressure (arm/cuff) and pulse rate were measured routinely four times daily after 15 min of recumbency and again after 2 min of quiet standing. Pressor responses to tyramine hydrochloride (dosage expressed as the base) infused intravenously in isotonic NaCl solution at varying rates for 15-min periods were determined in two patients with essential hypertension and one with scleroderma in the resting (recumbent) state during placebo and treatment periods. Basal metabolic rate (BMR) was determined as previously reported (5). In patients with Raynaud's phenomenon we measured responses to cold stimuli objectively by determining finger pad skin temperatures with a skin thermocouple after a standard cooling stimulus; subjective responses to exposure in an environment at 4°C and 50% humidity in a walk-in refrigerator were also recorded. In the two patients with glaucoma, intraocular pressures, fluid dynamics, and outflow indices were determined by Dr. Vernon Wong, Ophthalmology Branch, National Institute of Neurological Disease and Blindness. The sediment of freshly voided urine specimens was examined microscopically for  $\alpha$ -MPT crystals. Routine hematological and chemical tests were performed by the Clinical Pathology Section of the Clinical Center.

The urinary excretion of catecholamines, total metanephrines, and vanillylmandelic acid (VMA) was determined as cited previously (4, 6). All three excretory indices of catecholamine production were measured in the patients with pheochromocytoma, but only VMA was measured in other patients. To rule out an effect of the drug on the pattern of urinary metabolite excretion, the fate of 1000  $\mu$ c of D,L-norepinephrine-7-<sup>3</sup>H hydrochloride (2.2 c/mmmole)<sup>2</sup> given intravenously over a 30-min period to a patient (S. M., Table I) with pheochromocytoma was studied both before and during treatment with 4000 mg of  $\alpha$ -MPT/day. Urine was collected for 24 hr and then extensively fractionated by column chromatography

for estimation of radioactivity in various metabolites (4).

## RESULTS

### Effects on catecholamine production

The effect on catecholamine production of the maximal dosage of  $\alpha$ -MPT employed in 22 patients with pheochromocytoma was determined by comparing the urinary excretion of the naturally occurring catecholamines (norepinephrine plus epinephrine) and their major metabolites during control periods and during drug administration (Table I). Using the sum of these indices it may be seen that we reduced catecholamine production by 20–79% by  $\alpha$ -MPT dosage ranging from 600 to 4000 mg (11–73 mg/kg)/day. In seven patients (T. W., R. K., A. A., S. M., D. S., J. L., and E. W.) the total excretion of catecholamines plus metabolites was reduced to normal or near normal (< 10 mg) levels. Patients with benign and malignant tumors responded similarly. In individual patients stepwise increments of dosage up to 1500 mg/day produced marked increases in inhibition, but at higher doses the decreases in catecholamine production generally were proportionally less. Catecholamine production was determined daily in a sufficient number of patients to indicate that the maximum effect of a given dosage regimen occurred within 2–3 days and catecholamine production returned to control levels within 3–4 days after withdrawal of drug (2, 3).

In 18 other patients in whom the biochemical effects of  $\alpha$ -MPT were studied catecholamine production was normal, and the sole index used to ascertain drug effect was the level of urinary VMA excretion. As shown in Table II, percentage reductions (20–74%) produced by  $\alpha$ -MPT in these patients were comparable to those observed in cases of pheochromocytoma, though the quantitative changes were much smaller. Generally, doses exceeding 1000 mg/day resulted in a decrease of VMA excretion of more than 50%. Several assays for total metanephrines indicated a similar reduction in excretion values, but the low levels of urinary catecholamines during drug therapy could not be assayed reliably even with modified methodology (4).

It was assumed in these studies that the daily urinary excretion of catecholamine metabolites is a valid index of catecholamine production rate in

<sup>1</sup> Supplied by Dr. Elmer Alpert, Merck & Co., West Point, Pa.

<sup>2</sup> New England Nuclear Corporation, Boston, Mass.

TABLE I  
Biochemical and Clinical Effects of  $\alpha$ -MPT in Patients with Pheochromocytoma

Urinary excretion*															
Patient	Age	Sex	Wt kg	Daily		Control				Therapy				% Reduction	Comments on clinical aspects
				$\alpha$ - MPT	Dose	CA	NMN	VMA	Total	CA	NMN	VMA	Total		
Benign	yr			g	mg/kg	mg/24 hr									
E. D.	57	F	47	0.6	11	2.31	9.4	22.6	34.3	1.86	8.1	17.5	27.5	20	Little change other than marked sedation during a short course (4 days) of therapy.
C. B.	39	F	51	1.2	24	2.30	11.8	30.3	44.4	0.60	6.8	14.0	21.4	52	Drug was added to chronic dibenzylamine therapy and resulted in apparent reduction of BP and incidence of hypertensive attacks; discontinued 3 days before surgery.
T. W.	59	M	62	1.5	24	1.47	11.9	29.2	42.6	0.16	2.7	6.0	8.9	79	Marked improvement in chronic congestive heart failure. Developed diarrhea on drug (see Case 4 comment).
R. K.	28	M	83	2.0	24	.17	3.7	8.8	12.7	0.14	2.7	5.3	8.1	36	Patient asymptomatic off therapy. BP reduced from 135/90 to 120/80 mm Hg on 2.0 g of $\alpha$ -MPT.
S. K.	73	F	44	1.5	34	1.11	32.7	48.6	82.4	0.59	19.8	33.3	53.7	35	Inconclusive brief study due to many somatic complaints also present during placebo therapy.
E. A.	55	M	58	2.0	35	3.62	25.1	60.4	89.1	1.32	16.1	30.2	47.6	47	After an acute myocardial infarction, was treated with dibenzylamine for 5 months and for 3 months with $\alpha$ -MPT also, BP reduced from 140/89 to 117/72 mm Hg with $\alpha$ -MPT despite concomitant reduction of dibenzylamine dose.
K. L.	31	M	85	3.0	35	1.16	28.9	59.0	89.1	0.99	21.2	35.0	57.2	36	Normotensive except for occasional attacks which were reduced in frequency and severity by $\alpha$ -MPT.
D. L.	34	M	80	3.5	38	0.82	4.9	17.6	23.3	0.29	2.8	8.3	11.4	51	Brother of K. L., also usually normotensive except for attacks. Frequency and severity of episodes reduced; persistent mild sedation during treatment.

\* Values shown are averages of determinations on at least 2 different days; therapy values are at the maximum daily dose used in each patient. CA, catecholamines (epinephrine plus norepinephrine as norepinephrine equivalent); NMN, normetanephrine plus metanephrine as normetanephrine equivalent; VMA, vanillylmandelic acid; BP, blood pressure; BMR, basal metabolic rate.

TABLE I (Continued)

Patient	Age	Sex	Wt kg	Daily		Urinary excretion*					Therapy		% Reduction	Comments on clinical aspects	
				$\alpha$ - MPT	Dose g	CA	NMN	VMA	Total	CA	NMN	VMA			Total
yr	mg/kg	mg/24 hr													
A. A.	65	M	77	3.5	39	0.53	3.4	16.0	33.0	0.11	0.8	3.2	4.1	79	Decreased incidence and severity of attacks with reduction in average BP from 180/120 to 150/90 mm Hg despite discontinuation of chronic dibenzylamine therapy.
D. K.	64	F	50	2.0	40	0.34	9.5	20.2	30.0	0.18	7.5	12.0	19.7	34	Normotensive off therapy except for attacks. Felt very well on dose of 2.0 g of $\alpha$ -MPT with reduction of sweating, palpitations, and attacks. BMR reduced from +30% to +15%. Had slight diarrhea during treatment.
E. L. H.	42	F	55	2.5	45	2.57	7.5	22.6	32.7	0.46	3.4	6.5	10.4	68	Slight decrease in BP but marked decrease in incidence and severity of attacks. At 2.5 g of $\alpha$ -MPT developed neurological side effects (see Case 1 comment).
F. M.	57	M	67	3.5	45	1.05	10.7	44.6	56.4	0.16	5.4	12.4	18.0	68	Diagnosis made after acute myocardial infarction. BP reduced from 210/110 to 155/90 mm Hg on 3.5 g of $\alpha$ -MPT; because of anxiety and fatigue dose reduced to 2.0 g and therapy supplemented with small doses of dibenzylamine for 5 months until surgery.
S. M.	25	M	78	4.0	51	2.0	3.0	15.2	20.2	0.29	1.3	4.5	6.1	70	Decreased BP, sweating, and attacks; dry mouth and anxiety at 4.0 g of $\alpha$ -MPT dose.
J. D.	13	M	35	2.5	71	2.16	9.1	21.7	33.0	0.97	4.7	9.7	15.4	53	BP reduced from 187/129 to 155/104 mm Hg on 2.5 g; dose had to be reduced to 2.0 g due to tremor and anxiety.
B. B.	24	F	48	3.5	73	5.75	13.3	38.7	57.8	1.07	5.6	14.8	21.5	63	BP reduced from 185/115 to 160/93 mm Hg despite discontinuation of dibenzylamine. Complete remission of symptoms of headache, sweating, anxiety, and palpitations.
Malignant															
D. B.	33	M	70	2.0	29	0.87	2.2	10.5	13.6	0.30	1.5	5.0	6.8	50	Only mildly hypertensive, had slight reduction in BP but marked decrease in sweating.

TABLE I (Continued)

Patient	Age	Sex	Wt kg	Daily			Urinary excretion*				% Reduction	Comments on clinical aspects				
				$\alpha$ -MPT	Dose g	mg/kg	Control						Therapy			
							CA	NMN	VMA	Total			CA	NMN	VMA	Total
J. L.	23	M	65	2.0	31	0.59	4.2	13.1	17.9	0.26	2.2	6.5	8.0	53	Normotensive and asymptomatic off therapy. Slight decrease in BP and moderate persistent sedation were noted at 2.0 g dose.	
W. L.	19	M	60	2.0	33	4.4	40.1	113.	157.5	1.56	23.3	64.8	89.7	43	Rapidly growing tumor with intracranial metastases. Patient developed severe anxiety, tremor, trismus with drooling, and bizarre thoughts on 2.0 g dose.	
E. H.	63	M	42	2.0	48	8.3	25.0	72.8	106.1	0.21	4.9	18.2	23.3	78	Remarkable response to therapy (see Case 2 comment).	
E. D.	15	F	49	2.5	51	1.42	10.0	27.1	37.4	0.63	4.5	9.0	14.1	62	Asymptomatic on dibenzylamine. BP remained normal during treatment despite reduction of dibenzylamine dose from 80-20 mg/day.	
E. W.	28	M	74	4.0	54	2.0	7.1	23.0	32.1	0.55	1.4	7.6	9.6	70	Marked decrease in frequency and severity of attacks with average BP reduced from 185/118 to 146/99 mm Hg. Slight diarrhea at 4.0 g dose (see Case 3 comment).	
K. K.	14	F	46	3.0	65	1.99	8.6	26.8	37.4	0.64	4.3	10.1	15.0	60	Apparent resistance to dibenzylamine (160 mg/day) after 4 yr of therapy. Persistent sedation at 3.0 g of $\alpha$ -MPT dose level; only slight BP effect despite obvious chemical effect.	
Normal values										<0.1	<1.3	<6.8	<8.2			

TABLE II  
*Effect of  $\alpha$ -MPT on Urinary Excretion of VMA in Patients with Normal Catecholamine Production*

Patient	Age	Sex	Wt	Avg daily $\alpha$ -MPT dose		Urinary VMA		% Re- duction
				mg	mg/kg	Control* $\alpha$ -MPT*		
Essential hypertension								
F. D.	55	F	81	0.8	10	4.1	2.2	46
A. N.	38	F	66	0.8	12	4.2	2.6	38
V. G.	56	F	56	0.8	14	3.0	2.4	20
D. F.	52	M	65	1.2	18	3.1	1.2	61
F. B.	48	F	56	1.6	29	3.5	1.5	57
S. C.	58	F	50	1.6	32	3.4	0.9	74
E. B.	59	F	48	1.7	35	2.2	0.8	64
G. D.	29	F	54	2.0	37	4.2	2.0	53
G. E.	47	F	71	3.0	42	4.3	1.9	66
D. E.	43	F	46	2.0	43	3.7	2.1	43
E. H.	53	F	68	3.0	44	4.8	2.3	52
A. M.	50	F	57	3.0	53	4.2	1.7	60
Open angle glaucoma								
K. G.	56	M	78	1.0	13	4.3	3.0	30
Thyrotoxicosis								
F. A.	23	M	67	3.0	45	3.1	1.2	61
Raynaud's phenomenon								
L. I.	67	F	70	2.0	29	4.0	1.7	58
J. S.	43	F	64	2.0	31	3.2	1.7	47
L. P.	23	F	45	2.0	44	3.2	1.6	50
J. M.	28	F	52	2.0	48	4.4	1.7	61

\* Values are averages of determinations on at least two separate 24-hr collections.

the patient during placebo and treatment periods. The possibility that  $\alpha$ -MPT might alter over-all metabolism of circulating catecholamines and thereby distort urinary excretory patterns was eliminated by a study of the fate of radioactive norepinephrine given intravenously on two occasions to a patient with pheochromocytoma. As shown in Fig. 1, the excretion pattern of the radioactive metabolites during control and treatment periods was similar.

#### Therapeutic evaluation

Striking beneficial effects were observed in many of the patients with pheochromocytoma (Table I). Most patients experienced a decreased frequency and severity of hypertensive attacks, sweating, and palpitations. Blood pressure reduction of varying degrees was evident in all of the patients with pheochromocytoma who were hypertensive during control periods (18 of 22 cases).

In patients who were receiving phenoxybenzamine it was usually possible to reduce or discontinue use of this drug coincident with administration of  $\alpha$ -MPT. As reported previously (2, 3), blood pressure decreased progressively during the first 2 days of therapy with  $\alpha$ -MPT and, except for those patients who received  $\alpha$ -MPT to the day of surgery, there was a gradual increase to pretreatment values within 2-3 days after withdrawal of the drug.

13 patients received  $\alpha$ -MPT to the time of surgery. It was our clinical impression that these patients presented fewer intraoperative problems with blood pressure control than other similar patients who had not been so treated, and the surgeon was able to handle the tumor directly with less hazard of hypertensive crisis. Because of the marked variability in clinical features of the patients with pheochromocytoma, four cases will

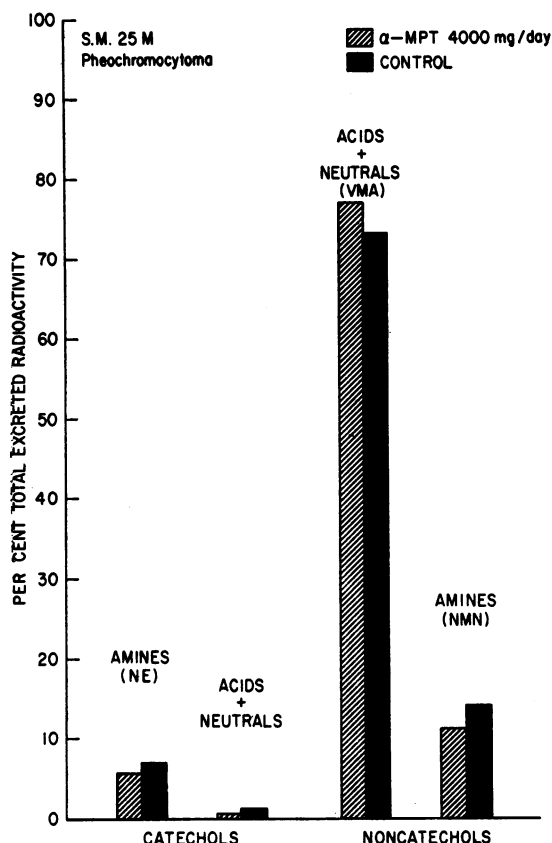


FIGURE 1 Excretion of radioactivity in various column chromatographic fractions of a urine specimen collected for 24 hr after infusion of norepinephrine- $^3\text{H}$  in a patient with pheochromocytoma. Two studies were done, one during a control period and the other during treatment with 4000 mg of  $\alpha$ -MPT daily. Total excretion of radioactivity was 75–80% in 24 hr, and the percentage of this distributed in various fractions was not altered by drug treatment. As indicated, the catecholamine fraction is composed primarily of norepinephrine (NE), the noncatechol acids plus neutral fraction is largely vanillylmandelic acid (VMA) and the noncatechol amines represent normetanephrine (NMN).

be described in detail to illustrate specific responses.

#### Illustrative cases of pheochromocytoma

**Case 1.** A 42 yr old female house painter (E. L. H.) had a  $2\frac{1}{2}$  yr history of “spells” characterized by a feeling of weakness, faintness, palpitations, sweating, and nervousness. These attacks were noted especially when she stretched to paint high above her head or in tight places. Her blood pressure was found to be markedly elevated at

times, and the level of urinary VMA excretion was diagnostic of pheochromocytoma. On admission to the N.I.H. she was found to be an anxious, perspiring, woman with blood pressure of 160/102 mm Hg while supine and 145/100 mm Hg while standing. Therapy with  $\alpha$ -MPT was started at a daily dose of 1000 mg; the patient reported a marked decrease in sweating within 24 hr. At a dose of 1500 mg/day she noted a decrease in anxiety as well as a marked reduction in the incidence of attacks. While receiving a dose of 2500 mg/day for 4 days she experienced the onset of a mild tremor of her hands and some “tightness” of her mouth; the dose was reduced to 2000 mg/day and these symptoms disappeared within 24–36 hr. During a predrug placebo period of 3 wk her blood pressure ranged from 140–225/80–140 mm Hg with a mean value of 184/108 mm Hg, and while receiving 2500 mg of  $\alpha$ -MPT daily it ranged from 120–200/80–130 mm Hg with a mean value of 167/107 mm Hg. Three measurements of BMR during the placebo period were at +35, +38, and +45%, and two determinations while she was receiving 2000 mg of  $\alpha$ -MPT per day were normal at +7 and +8%. During therapy with  $\alpha$ -MPT her urinary excretion of catecholamines plus metabolites was reduced by 68% to only slightly abnormal values (Table I). The patient received 2000 mg/day to the time of surgery. No phentolamine was required during the intraoperative period, and the highest blood pressure observed during removal of a pheochromocytoma of the left adrenal was 180/105 mm Hg.

**Comment.**  $\alpha$ -MPT controlled attacks and reduced sweating and BMR in this case. Though blood pressure was reduced only moderately, the drug apparently prevented the occurrence of hypertensive attacks during surgery. At a dose of 2.5 g/day, there was early evidence of neurotoxicity (tremor and “tightness” of mouth) which disappeared on reduction of dosage.

**Case 2.** A 63 yr old man (E. H.) probably had symptoms of pheochromocytoma since 1927 when he had recurrent headaches, hypertension, and a subarachnoid hemorrhage. He was treated symptomatically over the interim despite two other episodes of subarachnoid hemorrhage in 1944 and 1949. In 1955 he developed “diabetes” requiring insulin therapy, and in 1958 the diagnosis of pheo-



chromocytoma was made; all signs and symptoms including those of "diabetes" disappeared after surgical resection of his right adrenal gland which contained a pheochromocytoma. 6 yr later re-exploration because of recurrent hypertensive attacks and glycosuria revealed metastatic pheochromocytoma. His condition deteriorated, and in January 1966 he was transferred to the N.I.H. because of intractable hypertension and a 30 kg weight loss due to nausea and vomiting with abdominal bloating and obstipation. On admission the patient appeared moribund; his abdomen was massively distended with huge feces-filled loops of

atonic large bowel. The blood pressure was 180/120 mm Hg despite phenoxybenzamine therapy, and he was confused mentally. Striking peripheral cyanosis of the hands, feet, and prepatellar regions was observed, and the skin of some of these areas was ulcerated and sloughing due to intense cutaneous vasoconstriction (Fig. 2). Small doses of  $\alpha$ -MPT were started several days after admission and within 24 hr striking clinical changes were noted. The peripheral cyanosis disappeared and the ulcers began to heal rapidly (Fig. 2). He became much more alert mentally, and his blood pressure decreased from 180/125 mm Hg to

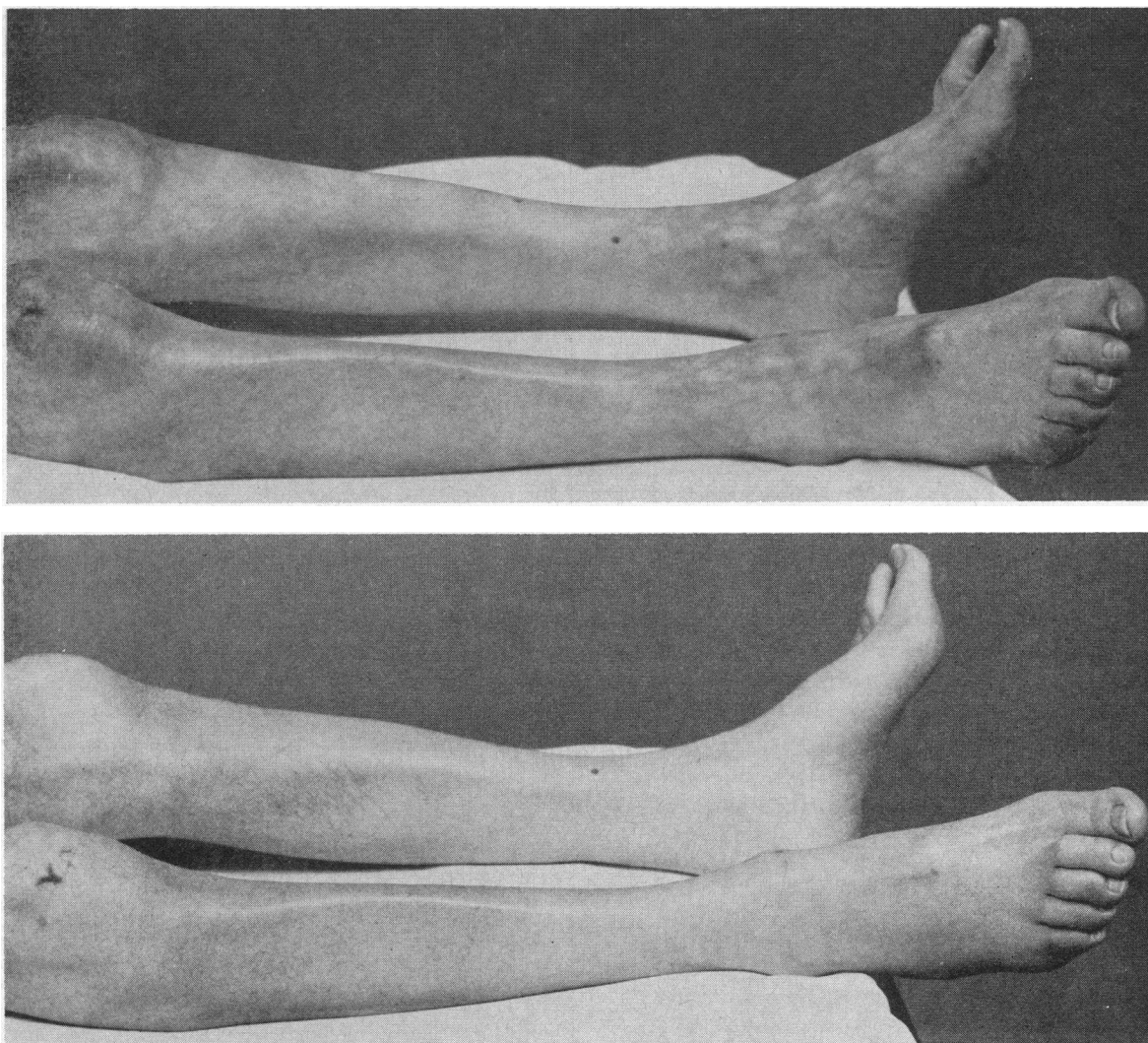


FIGURE 2 Appearance of the lower extremities of a 63 yr old man (E. H.) with malignant pheochromocytoma, before (upper) and 2 days after (lower) institution of treatment with  $\alpha$ -MPT in a dose of 750 mg/day. After starting  $\alpha$ -MPT cyanosis disappeared and healing of the ulcerated areas was apparent.

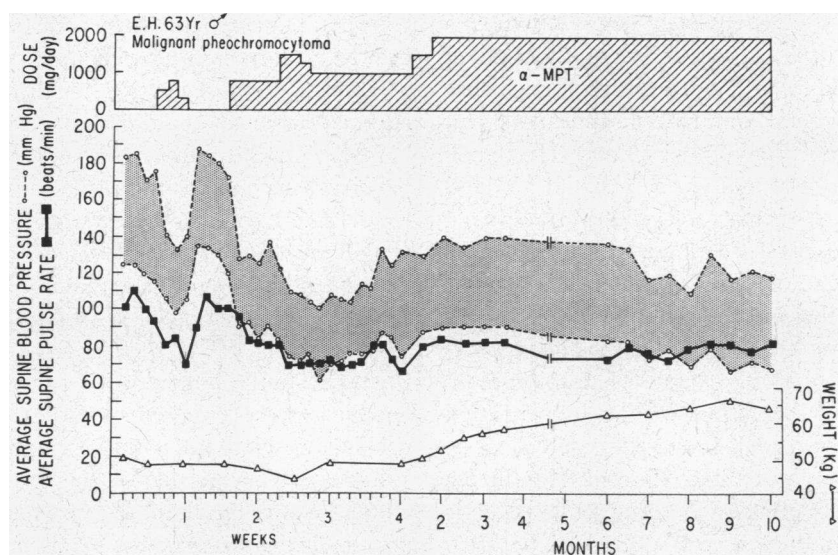


FIGURE 3 Effects of therapy with  $\alpha$ -MPT in a 63 yr old man (E. H.) with malignant pheochromocytoma. Prompt lowering of blood pressure and pulse rate to normal levels was achieved and maintained for 10 months, accompanied by an eventual weight gain of almost 20 kg.

135/100 mm Hg (Fig. 3). To establish that these striking changes were drug-related, we discontinued the  $\alpha$ -MPT and substituted it with placebo. His clinical condition reverted promptly to pretreatment status. Therapy with  $\alpha$ -MPT was quickly reinstituted and the patient again improved remarkably. The previously sluggish bowel sounds became more active, and the patient evacuated more than 5 kg of feces, reestablished normal alimentation, and gradually became ambulatory. While receiving 2000 mg of  $\alpha$ -MPT per day his urinary VMA excretion was reduced by 75% from 72.8 to 18.2 mg/24 hr, and his fasting blood sugars were reduced from over 200 mg/100 ml to 70–100 mg/100 ml. During the next 3½ months he improved steadily with a net weight gain of more than 12 kg, and he was discharged on 2000 mg of  $\alpha$ -MPT per day, having a normal blood pressure and pulse rate (Fig. 3). He convalesced briefly at home, and then returned to work as a regional sales manager for a large corporation, rapidly increasing his time in the office from a mere daily appearance to 5–6 hr/day. 6 months after starting  $\alpha$ -MPT and while still showing evidence of continued improvement he returned to the N.I.H. for further study. He had gained an additional 5 kg in weight since discharge, and his blood pressure was still normal

with a complete absence of hypertensive attacks or sweating. 2 months later his condition gradually and then rapidly deteriorated because of complications of tumor growth, though no effects of excess catecholamine production were manifest at any time while receiving  $\alpha$ -MPT. The patient died 10 months after starting therapy with  $\alpha$ -MPT.

*Comment.* This response to  $\alpha$ -MPT was the most impressive of any observed in patients treated with this drug. The clinical improvement correlated well with a reduction of catecholamine production and persisted for the duration of therapy until just before death. The 10 months during which this patient received  $\alpha$ -MPT was by far the longest course of therapy in any patient to date; no evidence of toxicity or drug crystalluria was detected at any time. The experience in this patient revealed  $\alpha$ -MPT to be potentially an excellent medical means of treating patients with inoperable pheochromocytoma.

*Case 3.* A 27 yr old minister (E. W.) had a left adrenalectomy for pheochromocytoma in January 1965. Because his blood pressure did not return to normal postoperatively and because of a progressive increase in blood pressure with recurrence of excessive sweating and headaches he was referred to the N.I.H. in April 1966. On admission the patient was a well developed anxious

man who perspired excessively and who had a marked rubor of the palmar and dorsal aspects of his hands. This rubor had been present before his previous surgery and had disappeared temporarily after resection of his tumor. His blood pressure was 196/130 mm Hg supine and 160/108 mm Hg standing. During a placebo control period the supine blood pressure ranged from 150–228/50–150 mm Hg.  $\alpha$ -MPT was started, and after the 2nd day of therapy at 2000 mg/day he noted a marked diminution of sweating and disappearance of the erythema of his hands. The blood pressure responded favorably to  $\alpha$ -MPT administration and was reduced from an average control value of 185/118 mm Hg to 146/99 mm Hg during treatment with 4000 mg of the drug (Fig. 4). His catecholamine production was decreased by 70% (Table I). At the time of surgery he was found to have metastatic tumor which was resected from around the left renal pelvis and the aorta. After surgery, urinary catecholamines and metabolites were still higher than normal, and his blood pressure remained elevated in the range of 150/115 mm Hg, which indicated residual tumor. He was discharged on phenoxybenzamine (20 mg daily) which maintained his blood pressure at about 135/90 mm Hg.

*Comment.* This patient also demonstrated an excellent response to inhibition of catecholamine synthesis with  $\alpha$ -MPT. The striking rubor of the hands was a finding which we had not noted

before in patients with pheochromocytoma, and the change in this condition was the first manifestation of clinical improvement. Though the patient had residual tumor and mild hypertension after surgery it was elected to treat him with small doses of phenoxybenzamine rather than  $\alpha$ -MPT because of inadequate experience with the long-term effects of the new drug. Reinstitution of  $\alpha$ -MPT therapy may be necessary as the tumor grows and catecholamine production continues to increase.

*Case 4.* A 59 yr old retired porter (T. W.) was well until August 1965 when he noted the onset of severe symptoms of congestive heart failure followed a week later by the development of aphasia and severe diaphoresis and headaches for which he was hospitalized elsewhere. A diagnosis of pheochromocytoma was made, and a large right superior mediastinal mass found on chest roentgenography was thought to represent an intrathoracic neurofibroma. 1 wk later he had the sudden onset of left hemiparesis and expressive aphasia which cleared within a week despite the finding on carotid arteriogram of a complete occlusion of the right middle cerebral artery. Hypertensive crises were controlled with oral phenoxybenzamine but because the patient developed congestive heart failure refractory to salt restriction and potent diuretics, he was referred to the N.I.H. for possible treatment with  $\alpha$ -MPT in an attempt to reverse his presumed catecholamine cardiomyopathy (6). On admission the patient

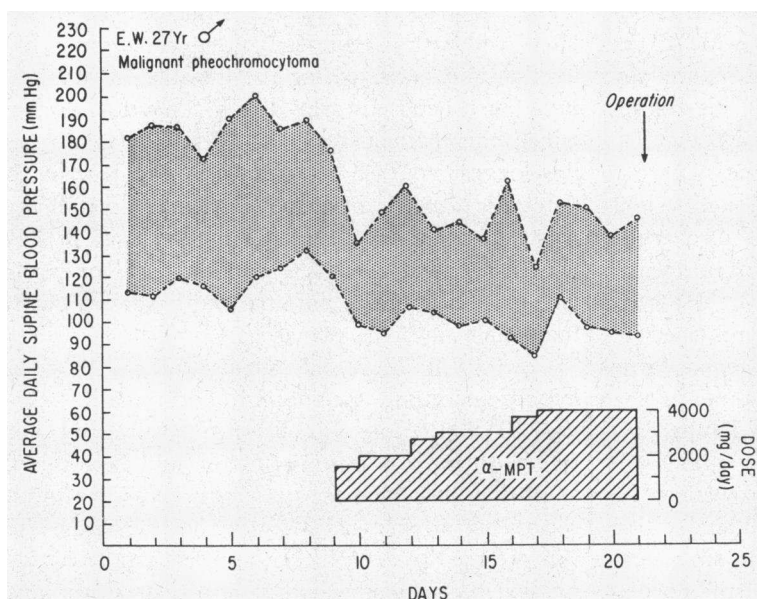


FIGURE 4 Blood pressure response to  $\alpha$ -MPT therapy in a 27 yr old man (E. W.) with malignant pheochromocytoma.

was an elderly, chronically ill Negro male who had a moderate expressive aphasia and residual weakness of the left leg and arm. His blood pressure was 100/60 mm Hg supine and 96/44 mm Hg standing; the pulse rate was irregular at 120/minute. The external jugular veins were distended 5 cm above the clavicle at 45°, and there were prominent A waves in the venous pulse. Dullness to percussion and egophony were present over the mid and upper paravertebral areas of the right thorax, and rales were heard at both lung bases. The heart was enlarged to the anterior axillary line and a loud protodiastolic gallop was heard. A tender liver edge was felt 3 cm below the right costal margin; there was a trace of ankle edema. Because of persistent hypotension in the range of 80–90/50–60 mm Hg the phenoxybenzamine was discontinued, digoxin dosage of 0.5 mg/day was discontinued because of multiple atrial and nodal arrhythmias, and  $\alpha$ -MPT therapy was started. When the evidence of digitalis toxicity disappeared, digoxin was resumed in a maintenance dose of 0.125 mg/day. On an  $\alpha$ -MPT dose of 500–750 mg/day the patient's blood pressure was in the range of 100–120/60–80 mm Hg, and he was free of hypertensive attacks and excessive sweating. Diuretic therapy was discontinued and salt restriction was ended without the recurrence of congestive failure. During his first 2 months in the hospital the  $\alpha$ -MPT dose varied between 500–1500 mg/day. 2 months after starting  $\alpha$ -MPT and while receiving a dose of 1500 mg/day the patient noted the onset of watery bowel movements. An extensive search for the etiology of the diarrhea was unsuccessful and he was treated symptomatically with anticholinergic and opiate drugs and a low roughage diet. It was then decided to withdraw the  $\alpha$ -MPT. Within 24–36 hr the patient developed dyspnea, tachycardia, sweating, and blood pressure elevation to 142/112 mm Hg, the highest blood pressure observed thus far during his hospitalization. The diarrhea decreased over the next several days, and phenoxybenzamine was given to control the blood pressure although it did not control his heart rate which had risen from 84 to 140 beats/min after the withdrawal of  $\alpha$ -MPT. Because he still was having 2–3 loose bowel movements daily and had a nodal tachycardia at 130–140 beats/min a week after withdrawal of  $\alpha$ -MPT, the drug was reinstituted. The

pulse rate and rhythm returned to normal within 24 hr. The watery diarrhea which persisted was treated symptomatically as before, and the patient, free of congestive heart failure, underwent surgery for an intrathoracic pheochromocytoma 3 months after starting on  $\alpha$ -MPT therapy. During the postoperative period the patient had mild diarrhea for the first 10–14 days, and this then gradually abated. The excretion of catecholamines and metabolites returned to normal postoperatively.

*Comment.*  $\alpha$ -MPT produced an excellent therapeutic response in this patient with catecholamine cardiomyopathy due to an intrathoracic pheochromocytoma. Tachycardia and arrhythmias which were controlled by  $\alpha$ -MPT recurred during temporary substitution of phenoxybenzamine, perhaps because the beta adrenergic effects of circulating catecholamines were unaffected by the  $\alpha$ -adrenergic-blocking drug. Diarrhea occurred in this patient in association with  $\alpha$ -MPT treatment. This patient was most unusual in that his tumor, arising remote from the adrenal glands, produced large amounts of epinephrine (30% of urinary catecholamine excretion, Table I) as well as norepinephrine.

In addition to the aforementioned therapeutic evaluation of  $\alpha$ -MPT in pheochromocytoma, it seemed important to ascertain whether the drug might be a useful antihypertensive agent in cases of essential hypertension. As noted previously (Table II) in patients with the latter condition in whom catecholamine production is normal, the drug produces a degree of inhibition of catecholamine biosynthesis (as indicated by urinary VMA) comparable to that observed in pheochromocytoma. Nonetheless, the effects of  $\alpha$ -MPT on the blood pressure of patients with essential hypertension was much less striking than in pheochromocytoma. While the effects of  $\alpha$ -MPT were studied in 20 cases of essential hypertension, the results in 7 patients will not be presented since they were inconclusive either because of relatively low dosage (< 1500 mg/day) or brief duration of treatment (< 1 wk). Effects of the drug as sole treatment in eight patients, and on addition to existing suboptimal treatment with an accepted antihypertensive drug in six patients, are summarized in Table III. A convincing antihypertensive effect was noted in only three patients in whom the drug was used alone (patients M. D.,

TABLE III  
Blood Pressure Effects in Patients with Essential Hypertension Given  $\alpha$ -MPT Alone,  
or in Combination with Standard Antihypertensive Drugs

Patient	Avg dose $\alpha$ -MPT  <i>mg/day</i>	Average blood pressure*						Other antihypertensive therapy, all periods
		Supine			Standing			
		Precontrol	$\alpha$ -MPT	Postcontrol	Precontrol	$\alpha$ -MPT	Postcontrol	
		<i>mm Hg</i>						<i>mg/day</i>
Sole therapy								
M. D.	2000	150/105	130/88	141/105	155/112	126/94	147/106	—
G. D.	1700	177/116	159/107	168/115	164/115	144/101	149/112	—
G. E.	3000	166/115	141/99	150/107	151/110	137/101	145/108	—
E. F.	1500	188/123	168/108	186/122	166/122	128/85	158/113	—
F. D.	3000	192/120	187/121	—	174/114	170/118	—	—
R. L.	3000	166/116	157/109	—	152/114	154/116	—	—
E. B.†	1700	158/113	143/101	—	175/130	120/87	—	—
A. M.	3000	174/113	171/106	181/117	162/109	160/113	169/113	—
Combined therapy								
E. B.†	900	151/107	132/96	147/106	151/116	119/95	149/116	Methyldopa 750
J. P.	1600	209/99	196/95	204/101	145/79	115/66	151/85	Guanethidine 87.5
R. R.	3000	154/109	147/100	159/111	142/108	118/94	138/108	Reserpine 0.25
W. S. M.	700	181/123	175/121	183/123	155/113	131/92	145/108	Methyldopa 500
A. B.	2500	161/110	147/99	—	144/105	133/96	—	Methyldopa 500
A. L.	3000	173/122	144/98	153/106	169/126	127/91	145/109	Hydrochloro- thiazide 100

\* Each value is average of four daily determinations for the last 5 days of each period.

† Same patient.

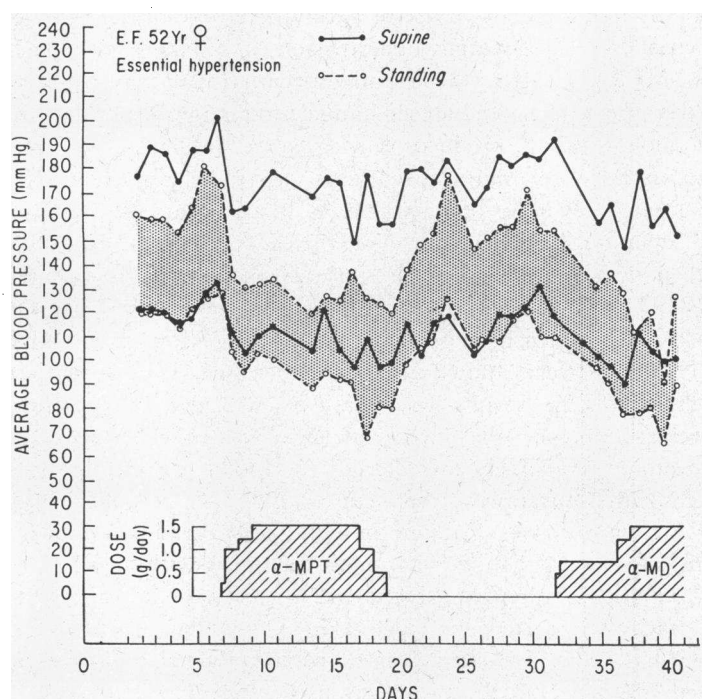


FIGURE 5 Comparison of the effects of equivalent doses of  $\alpha$ -MPT and methyldopa ( $\alpha$ -MD) on the blood pressure of a woman with essential hypertension.

E. F., and E. B.), blood pressure lowering occurring in both the supine and standing positions. A comparison of the effects of 1.5 g of  $\alpha$ -MPT with that of an equivalent daily dose of methyldopa in patient E. F. is shown in Fig. 5. Blood pressure lowering with the two drugs was comparable in this case, with an orthostatic effect predominating. In contrast to the situation when the drug was used alone, each of the six patients who was receiving guanethidine, reserpine, methyldopa, or hydrochlorothiazide exhibited a blood pressure response when  $\alpha$ -MPT was added to the ongoing drug regimen (Table III). Under these circumstances, blood pressure lowering was evident with doses as low as 700 mg/day and was generally greater in the standing than supine position.

No convincing therapeutic effect of  $\alpha$ -MPT could be established in the patients with glaucoma, migraine, thyrotoxicosis, or Raynaud's phenomenon and none of these normotensive subjects became hypotensive on  $\alpha$ -MPT. The two patients with open angle glaucoma received daily drug doses of 500 and 1000 mg respectively, for up to 4 wk. In the patient with migraine headache (a 49 yr old woman), a complete cessation of migraine attacks (usual frequency two times per week as an outpatient, two attacks also occurring during the 1st wk of hospitalization which served

as control period) occurred coincident with administration of  $\alpha$ -MPT in a dosage range of 0.5–0.75 g for 17 days. The patient was also obviously sedated during this time. Migraine attacks recurred within 1 wk as drug dosage was decreased to 0.1 g/day and then discontinued. A patient who had severe thyrotoxicosis (serum protein bound iodine of 16.3  $\mu$ g/100 ml and  $^{131}$ I uptake of 60% at 24 hr) was treated with up to 4000 mg of  $\alpha$ -MPT daily for a total of 12 days. Neither the average daily resting pulse rate nor the BMR was altered significantly by this therapy despite a reduction of VMA excretion of 61% (Fig. 6). This patient was moderately sedated, but there was no other sign of beneficial effect. Four of the six patients with Raynaud's phenomenon initially showed suggestive beneficial effects while receiving 1.0–2.0 g of  $\alpha$ -MPT per day. Subjectively these patients claimed an increase in tolerance to cold exposure in that a longer exposure elapsed before the development of pain in the hands. This effect tended to persist on switching to placebo medication, however, and it was impossible to demonstrate any increase in skin temperature.

#### Other drug effects

Central nervous system effects were noted almost uniformly in patients of all categories. Seda-

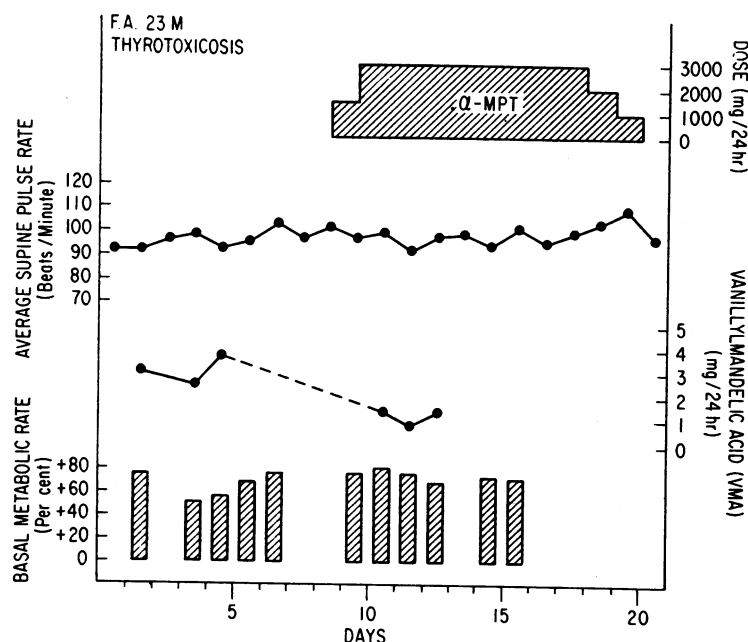


FIGURE 6 Effects of therapy with  $\alpha$ -MPT in a 23 yr old male with severe thyrotoxicosis. Though the VMA excretion was reduced by 60% to levels of only 1 mg/day, there was no effect on resting pulse rate or the basal metabolic rate.

tion, generally mild but of varying degree, was observed in 44 of the 46 subjects in this study who received a dose of 1000 mg or more  $\alpha$ -MPT daily; several patients experienced sedation with daily doses as low as 300–600 mg. Sedative effects began within 18–24 hr of institution of treatment with divided daily dosage, were maximal at 2–3 days, waned during the next few days, and usually were not obvious after 1 wk unless dosage was increased. At doses greater than 2.0 g/day some degree of sedation or feeling of fatigue tended to persist. Interestingly, patients who received single 1.0 g oral doses for study of the drug's metabolism (4) did not experience sedation though this effect occurred uniformly when the same total dose was divided over a 24 hr period.

Other central effects observed included an anxiety or agitated depression and changes in sleep pattern after withdrawal of medication. Anxiety was noted in four cases of pheochromocytoma (F. M., S. M., J. D., and W. L., Table I) at doses of 2.0–4.0 g of  $\alpha$ -MPT per day, which necessitated reduction of dosage or cessation of treatment. The study group of patients with essential hypertension was unusual in that six subjects had a history of psychic depression. Three of these six patients became sufficiently agitated on 1.0–2.0 g of drug daily to require stopping treatment. One patient with Raynaud's phenomenon became anxious at the 2.0 g dose level. Temporary changes in sleep pattern on withdrawal of drug occurred in most patients who had experienced sedative effects; these changes consisted of a pleasant feeling of alertness and ambition accompanied by insomnia for 48–72 hr.

In addition to changes in mood and mental activity, adverse effects related to neuromuscular activity appeared in three patients with pheochromocytoma (two of whom were also quite anxious) and two of the patients with essential hypertension who had manifested an agitated state. The mildest alterations consisted of fine tremor of the hands first manifest as a change in handwriting and in severest form consisted of gross tremor of the hands and legs unaffected by rest or movement and accompanied by tightening of the jaw with trismus and plastic resistance to passive movement. The patient who had the most severe reaction had intracranial metastases from a pheochromocytoma and developed severe sympto-

matology at a dose of 2.0 g/day (W. L., Table I). As with mood changes, neuromuscular effects disappeared rapidly with cessation or reduction of drug dose. Patients exhibiting neuromuscular effects had deep tendon reflexes and plantar responses unchanged from control status.

Other side effects observed were diarrhea (five cases), galactorrhea (1 case), and decreased salivation with "dry" mouth (one case). Diarrhea was of minimal degree except in one of the patients with pheochromocytoma (T. W., Case 4) and in a patient with scleroderma who had a history of mucus colitis and developed flatulence with frequent, watery bowel movements while receiving 2.0 g of  $\alpha$ -MPT per day. Symptoms abated in the latter subject when the drug was stopped for 3 days, but diarrhea recurred on rechallenge with  $\alpha$ -MPT. Galactorrhea occurred in a 43 yr old woman with Raynaud's phenomenon at an  $\alpha$ -MPT dose of 2.0 g; the patient had two children, 18 and 15 yr of age, and was menstruating normally at the time of study. Fluid could no longer be expressed from her breasts 10 days after discontinuing  $\alpha$ -MPT.

No other clinical findings could be attributed to  $\alpha$ -MPT. There was no crystalluria even at a dose of 4.0 g daily and no evidence of renal, hepatic, or hematological toxicity by the usual monitoring.

### Special studies

The question exists whether any of the effects of  $\alpha$ -MPT can be attributed to the minor degree of metabolism of the drug to  $\alpha$ -methyldopa (4). A few observations were made which bear on this question. Since the changes in sleep pattern after  $\alpha$ -MPT administration and withdrawal are very reminiscent of those observed with methyldopa (7), it may be pertinent that in three hypertensive patients (E. B., W. S. M., and A. B., Table III) central effects occurred with  $\alpha$ -MPT that were seemingly independent of ongoing therapy with methyldopa. Patients W. S. M. and A. B. both became markedly sedated for the first few days of  $\alpha$ -MPT administration and then showed striking insomnia after its withdrawal despite the continuation of methyldopa therapy. The responses of E. B. differed in that she was sedated initially on 750–1000 mg of  $\alpha$ -MPT, but as the dose was continued she developed insomnia and anxiety which regressed when  $\alpha$ -MPT was discontinued;



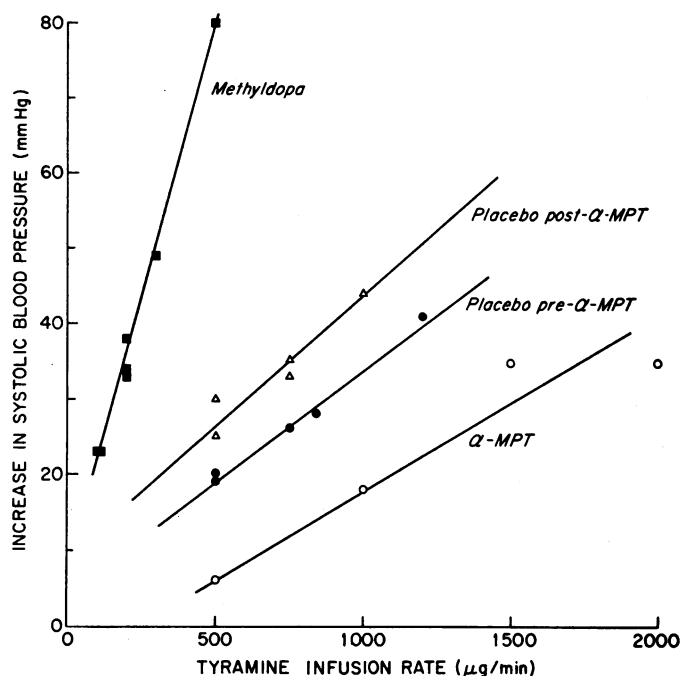


FIGURE 7 Alterations in pressor responsiveness to tyramine produced by equivalent doses of  $\alpha$ -MPT and methyldopa in a hypertensive patient (E. F.). Individual values represent systolic pressure increments produced by 15-min intravenous infusions of tyramine at the rates indicated. The protocol of drug administration is that depicted in Fig. 5; tyramine testing was done on the 9th and 11th days of  $\alpha$ -MPT treatment and on the 7th and 10th days of methyldopa therapy.

on the other hand, 12 days later when methyldopa was discontinued the patient again experienced transient pronounced insomnia.

Evidence against the participation of methyldopa in the peripheral sympathetic effects of  $\alpha$ -MPT was obtained by the demonstration that pressor responses to the indirectly acting pressor amine, tyramine, were reduced by  $\alpha$ -MPT treatment in the three subjects studied. An illustrative study is depicted in Fig. 7. The patient was a hypertensive subject (E. F.) who was studied during placebo periods and during periods of treatment with 1.5 g of  $\alpha$ -MPT and 1.5 g of methyldopa, respectively, with comparable reductions in blood pressure being achieved with the two drugs (see Fig. 5). As shown in Fig. 7, systolic pressor responses to varying rates of infusion of tyramine were decreased by approximately 50% during  $\alpha$ -MPT treatment. In contrast, treatment with methyldopa was accompanied by an enhanced responsiveness (300–400%) to tyramine.

## DISCUSSION

It is clear from the data presented that  $\alpha$ -MPT is effective in inhibiting catecholamine synthesis in man. This is true whether the rate of synthesis is high, as in pheochromocytoma, or normal as in cases of essential hypertension. Furthermore, the

degree of inhibition is similar with equivalent doses of drug in both circumstances.

Reductions of catecholamine synthesis over the wide range of 36–79% resulted in clear-cut improvement in the clinical condition of patients with pheochromocytoma. In most cases the results compared favorably with those achieved by administration of adrenergic-blocking drugs, and in some notable instances (Cases 2 and 4, above), the effects of  $\alpha$ -MPT were superior to those attainable with other drugs. Despite current availability of potent alpha and beta adrenergic-blocking drugs, it appears preferable and simpler to antagonize the wide range of "effects" of the catecholamines by actually reducing their production. With such an approach it is possible to achieve a balanced overall effect with maximum therapeutic benefit using a single drug.

In contrast to the situation in pheochromocytoma, in which symptomatology is directly related to catecholamine production rate, the sensitivity and specificity of response in conditions associated with normal rates of catecholamine synthesis were less apparent. Thus, it appears that inhibition of catecholamine biosynthesis to the extent of 50–70% in patients with essential hypertension was insufficient to result in consistent reduction of blood pressure. In contrast to our



initial impression (2), however, these additional studies indicate that blood pressure effects clearly occur in some patients. Furthermore, lowering of blood pressure can be produced consistently if the drug is added to ongoing therapy with an accepted antihypertensive agent.

Preliminary studies of  $\alpha$ -MPT effects in other conditions in which antagonism of sympathetic function has been used in therapy, but in which over-all catecholamine metabolism is normal, failed to reveal any therapeutic effects. No appreciable beneficial effects accrued to a single patient with thyrotoxicosis, a condition reported to be possibly associated with an increased sensitivity to catecholamines (8) and reported to be partially responsive to certain adrenergic antagonists (9-11). Results in two patients with open angle glaucoma and in one patient with migraine were difficult to interpret, and apparent subjective benefit in patients with Raynaud's phenomenon was considered to be no greater than that achievable with placebo. Further evaluation of patients with these and other diseases has been prohibited at least temporarily pending evaluation of results of toxicity studies in animals (see below).

A number of untoward effects were encountered in patients given  $\alpha$ -MPT. Persistent sedation or the development of an anxiety state, while not of serious consequence, limited the level of dosage which could be tolerated by some patients. This was not a serious problem in cases of pheochromocytoma, but was a significant deterrent in cases of essential hypertension, possibly because our study group was somewhat biased toward patients with a past history of psychic disturbances. The development of tremor in several patients, accompanied in two patients by "tightness of the mouth" or trismus, is of considerable interest. Though the clinical neurological states of these patients were not entirely characteristic of an extrapyramidal disorder, it seemed to us that there were similarities. Since depletion of 3,4-dihydroxyphenylethylamine (dopamine) in neurones of the basal ganglia has been found in association with extrapyramidal syndromes (12), it seems possible that we were observing such a circumstance as a result of  $\alpha$ -MPT. Dopamine is an intermediate in the biosynthesis of norepinephrine and would be expected to decrease in tissues of patients in whom tyrosine hydroxylase activity

was inhibited. As with symptoms of sedation and anxiety, tremors disappeared within a few days of reduced drug dose, a period during which catecholamine synthesis rate would have reverted towards normal. The appearance of lactation in a premenopausal patient probably also represented an effect of  $\alpha$ -MPT on the central nervous system. A wide variety of centrally acting anti-adrenergic drugs, including methyldopa, reserpine, and the phenothiazines have been reported to induce galactorrhea in women (13), presumably by interrupting adrenergic mechanisms which normally inhibit release of prolactin from hypothalamic centers.

The most troublesome untoward effect of the drug was severe diarrhea occurring in two patients. Ordinarily one might tend to attribute such diarrhea to diminished sympathetic neural control of the bowel, as occurs with guanethidine and similar drugs. However, one of the two patients still had excessive amounts of catecholamines due to pheochromocytoma, and diarrhea in both patients seemed to persist after drug withdrawal beyond the time required for return of catecholamine synthesis to control levels. The possibility of a direct irritant effect of the drug seems likely at this time since studies in dogs have shown that  $\alpha$ -MPT orally in a dose of 150 mg/kg per day may produce ulcerating lesions of the intestinal tract in as little as 2 wk.<sup>3</sup>

Because of drug crystalluria and urolithiasis occurring in dogs receiving as little as 50 mg/kg of  $\alpha$ -MPT per day,<sup>3</sup> therapeutic evaluation of  $\alpha$ -MPT has been markedly restricted. This accounts for the fact that our studies in essential hypertension are somewhat limited and those in the other states, in which there is a normal catecholamine production rate, are highly preliminary. However, no evidence of  $\alpha$ -MPT crystalluria has been found in any of our patients receiving up to 4000 mg of  $\alpha$ -MPT daily. There was no evidence of urolithiasis at postmortem examination of the patient (E. H.) who received 2000 mg of  $\alpha$ -MPT daily for 10 months. One of our patients (D. B., Table I) was treated subsequently with considerably larger doses of  $\alpha$ -MPT at another institution; crystalluria was noted at a dose of 5000 mg/day.<sup>4</sup> It should be noted that, in contrast with

<sup>3</sup> Bayne, G. M. Merck & Co. Personal communication.

<sup>4</sup> Melmon, K. Moffett General Hospital, San Francisco, Calif. Personal communication.

human subjects, dogs that developed evidence of  $\alpha$ -MPT crystalluria and stones were heavily sedated and ate and drank poorly. Similar toxicological studies in rats indicate that crystalluria and renal damage may be prevented by forced water intake (14). In vitro solubility studies show that despite its general insolubility in aqueous solutions  $\alpha$ -MPT is soluble in normal urine to the extent of slightly more than 1 mg/ml. Since absorption averages 60–70% of the oral dose (4) and usual urine output exceeds 1000 ml/day, one would not expect crystalluria in patients receiving up to 2000 mg/day. Furthermore, it is possible that in common with a number of other compounds, this drug may actually be excreted in urine in a supersaturated state with a much higher apparent solubility coefficient. Nevertheless, it is advised that any patients receiving larger doses of  $\alpha$ -MPT be encouraged to ingest enough liquids to excrete a daily urine volume of 2000 ml or more.

Though the primary effects of  $\alpha$ -MPT are thought to be due to inhibition of catecholamine biosynthesis, a small conversion of the drug to methyl dopa and its amine metabolites raises the question of the possible role of methyl dopa in the responses observed (4). The results of studies presented here tend to rule out a methyl dopa effect. It seems noteworthy that the initial sedative and later withdrawal effects of  $\alpha$ -MPT occurred in the usual way when the drug was administered to patients who were already receiving amounts of methyl dopa, 500–750 mg, that were massive compared to that which can originate from  $\alpha$ -MPT (4). As to the peripheral effects of  $\alpha$ -MPT, the demonstration that tyramine pressor responsiveness is decreased during  $\alpha$ -MPT whereas it is typically enhanced during methyl dopa therapy (15) as confirmed here in one of the patients, also argues strongly for inhibition of catecholamine synthesis as the primary mechanism of drug action.

A final consideration is what future exploration should be made in human subjects of the effects of  $\alpha$ -MPT itself, and of other drugs yet to be developed which inhibit tyrosine hydroxylase. Balancing the risks of toxicity vs. therapeutic benefit, it seems reasonable to continue to utilize  $\alpha$ -MPT in the therapy of malignant pheochromocytoma. Also, it seems that the drug can be given safely in the

hospital for the short periods of time required for preoperative preparation of a patient with benign pheochromocytoma. Though  $\alpha$ -MPT used alone appears not to be a safe and effective means of controlling the blood pressure of patients with essential hypertension, its effectiveness in combination with other antihypertensive drugs warrants further study. It is likely that even partial control of the rate of catecholamine biosynthesis with  $\alpha$ -MPT would favorably affect responsiveness to other antihypertensive drugs which interact with sympathetic mechanisms in a different way. Judging from studies in experimental animals (16), increased sympathetic activity resulting in marked increases in rates of catecholamine synthesis is one of the reactions to stressful stimuli. Such increases in synthesis rates can be eliminated by use of  $\alpha$ -MPT. Thus, insofar as variations in blood pressure may occur in reaction to "stress,"  $\alpha$ -MPT might have application in placing a "damper" on an important sympathetic neural mechanism. For these reasons, we would recommend that  $\alpha$ -MPT in doses up to 3.0 g/day be evaluated further in combination with other drugs in patients with essential hypertension. Pheochromocytoma and essential hypertension represent the minimal clinical spectrum in which more potent inhibitors of tyrosine hydroxylase might be clinically useful.

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